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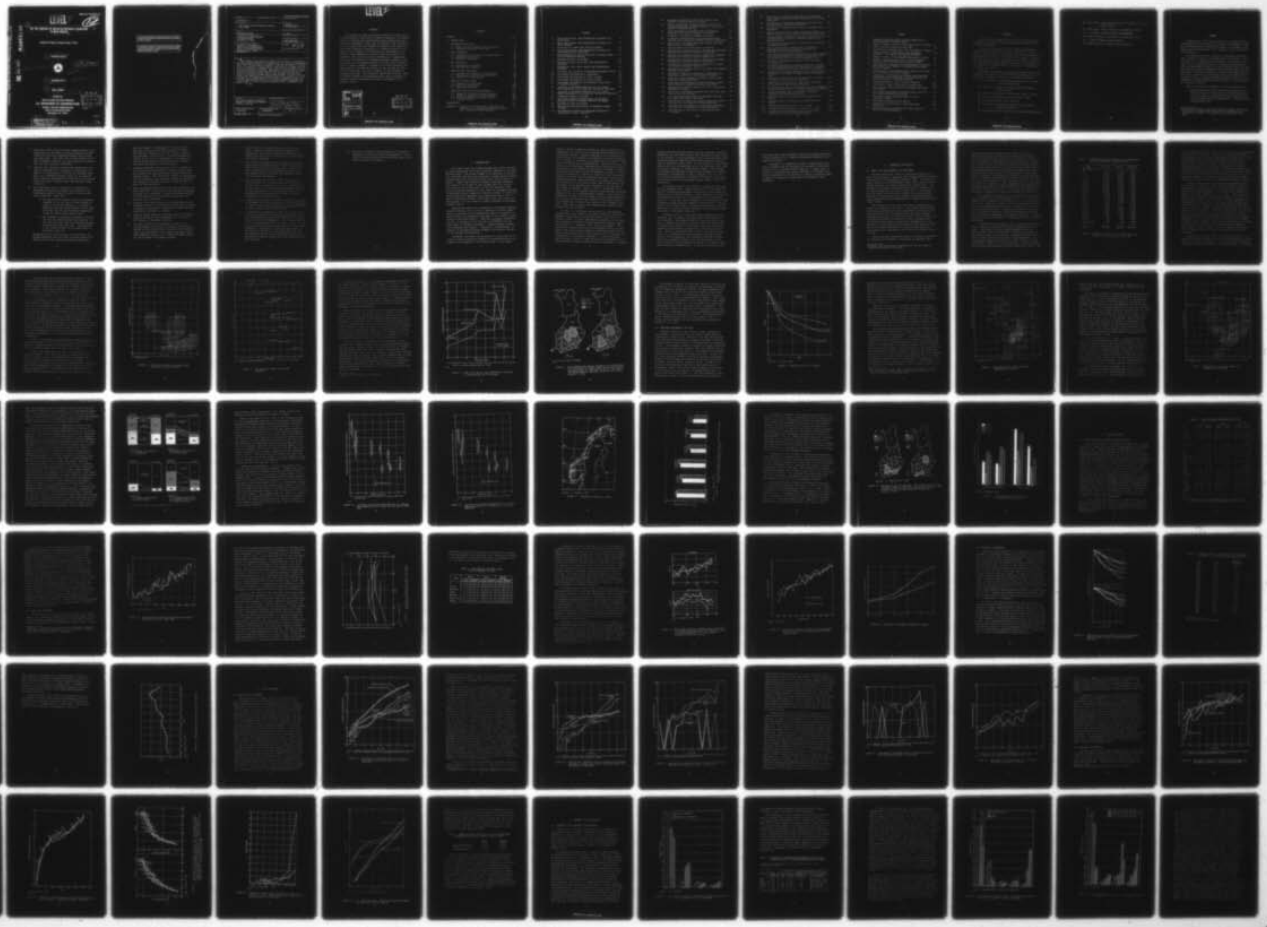

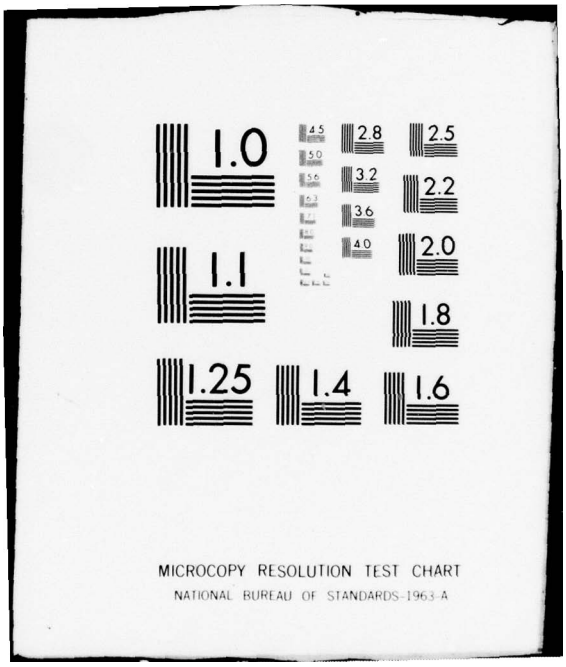
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LEVEL II

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ON THE LINKAGE OF SOLAR ULTRAVIOLET RADIATION TO SKIN CANCER

(Institute for Defense Analyses Paper P-1342)

Pythagoras Cutchis

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U.S. DEPARTMENT OF TRANSPORTATION

FEDERAL AVIATION ADMINISTRATION

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16. Abstract

The linkage of solar ultraviolet radiation to skin cancer is investigated in this paper by making comparisons of incidence rates in countries with predominantly white populations with respect to geographic, time, age, and anatomic site variations. It is concluded that the evidence in support of the hypothesis that solar ultraviolet radiation is a dominant factor in the induction of squamous cell and basal cell carcinomas is convincing. Many anomalies of various kinds are found in the hypothesis that solar ultraviolet radiation is a significant factor in the induction of malignant melanoma, leading to the conclusion that the primary cause(s) for this class of tumors must be sought elsewhere. Analysis of the data indicates that urbanization is an important factor in the etiology of basal cell carcinoma and, to a lesser degree, in the etiology of malignant melanoma. The biological amplification factor (ratio of percent increase in non-melanoma skin cancer incidence to percent increase in ultraviolet dose) is estimated to lie between 1 and 2.

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LEVEL II

ABSTRACT

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FOREWORD

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SUMMARY

Comparisons of skin cancer incidence in countries having a predominantly white population with respect to geographic, time, age, and anatomic site variations are made in an attempt to determine the characteristics of the linkage to solar ultraviolet (UV) radiation.

The hypothesis that an increase in ultraviolet radiation dose, lifetime or acute, is associated with an increase in the incidence of (1) squamous cell carcinoma, (2) basal cell carcinoma, and (3) malignant melanoma, is tested by investigating recent epidemiological data over a wide latitude band. The lifetime dose hypothesis is emphasized and generally implied in the discussion. Principal attention is given to malignant melanoma. One of the tests used to investigate ultraviolet radiation as a causative factor in malignant melanoma assumes validity of the hypothesis linking solar ultraviolet radiation to the incidence of "other skin cancer."*

Some of the principal findings of this investigation are:

1. The hypothesis that solar ultraviolet radiation is a dominant factor in the induction of squamous and basal cell carcinomas in predominantly white populations is strongly supported by an examination of available worldwide incidence data.

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*Denotes skin cancers other than malignant melanoma and assumed to consist of squamous plus basal cell carcinomas; "non-melanoma skin cancer" is a preferable but less widely used term.

2. A very large number of inexplicable anomalies of various kinds are found in the worldwide incidence data which are inconsistent with the hypothesis that solar ultraviolet radiation is a significant factor in the induction of malignant melanoma, leading to the conclusion that the primary cause(s) for this class of tumors must be sought elsewhere.

3. There is clear evidence of a latitude gradient for other skin cancer incidence on a worldwide basis; there is no similarly clear evidence of a latitude gradient for the incidence of malignant melanoma.

4. The ratio of the incidence of other skin cancer for males to that for females exceeds unity for all countries, and has a strong latitude gradient, increasing toward the equator; for malignant melanoma incidence this sex ratio may be slightly greater or smaller than unity with an average value of about 0.9, and has no apparent latitude gradient. For most geographic regions, the malignant melanoma sex ratio is less than unity, a finding which is inconsistent with the solar ultraviolet radiation hypothesis for malignant melanoma.

5. The incidence of malignant melanoma for males in Norway is 20 times higher than in Zaragoza, Spain. Since Norway is much farther from the equator than Spain, this finding contradicts the lifetime solar UV dose hypothesis. There is no evidence in the literature that such a large discrepancy (greater than 20) can be rationally attributed to ethnic differences in Caucasian populations. Neither Norway nor Zaragoza are singularities. Residents in all Mediterranean countries of Europe enjoy very low malignant melanoma mortality rates, while residents of all Scandinavian countries and Finland suffer high mortality rates.

6. Age-specific incidence curves for malignant melanoma differ fundamentally from those for other skin cancer. In recent years the risk for other skin cancer increases almost exponentially with age, while for malignant melanoma the risk is essentially the same for adults between approximately 40 and 65 years of age. The recent age-specific incidence curves for Connecticut and New Mexico are almost identical (Fig. 33). From these data it can be deduced that malignant melanoma incidence is not a significant function of lifetime dose or, in all likelihood, the number of acute UV doses received.

7. There has been a worldwide increase in the incidence of both other skin cancer and malignant melanoma in almost all countries with a predominantly white population. However, exceptions can be found. Squamous cell carcinoma incidence decreased in Finland from approximately 6 per 100,000 in 1960 to 3.5 in 1973, whereas malignant melanoma during this same period increased from 2 to 3.5 (Fig. 22). In Australia, mortality from malignant melanoma doubled from 1950 to 1964 but mortality from other skin cancer decreased by 50 percent during the same period (Fig. 37). These and other similar cases in which the time variations of incidence over a long period of time run in opposite directions constitute anomalies for the solar radiation hypothesis linking solar radiation to malignant melanoma.

8. Malignant melanoma mortality exceeds other skin cancer mortality for both males and females and has increased with time, whereas other skin cancer mortality has decreased with time. There is evidence in some countries of a latitude gradient for malignant melanoma mortality. Since malignant melanoma also occurs in younger age groups, it poses a far more serious problem to public health. Its causative factors are clearly in urgent need of being established.

9. Other skin cancer favors the most exposed anatomic sites (head and neck, and hands), whereas malignant melanoma favors the relatively unexposed anatomic sites (trunk and lower limb). The lower limb is more favored in the legs of females, however, and this finding is consistent with the solar radiation hypothesis.

10. Anatomic site frequency distribution changes with latitude for squamous cell carcinoma, but anomalously appears to be independent of latitude for malignant melanoma, e.g., malignant melanoma cases for the head and neck constitute approximately 18 percent of all melanoma cases in Finland, southern Texas, and Australia (Figs. 42 and 43).

11. Two dichotomies exist in anatomic site behavior for malignant melanoma which suggest the existence of two carcinogenic agents, neither of which is solar ultraviolet radiation. These are:

    A. The age-specific incidence rates for malignant melanoma in the face and foot were similar to those for other skin cancer, i.e., almost exponential with age, whereas those for the trunk and lower limb were approximately independent of age for adults older than 35 years.

    B. The incidence of malignant melanoma in the face and foot was invariant with time, whereas in the trunk and lower limb the incidence has been rising very rapidly with time. The beginning of the latter increase can be traced back to the 1880's (Fig. 52).

    The dating back of the increase in the postulated carcinogen associated with the trunk and lower limb to the 1880's rules out the frequently expressed hypothesis

that the changes in clothing and life styles since World War II and the resulting increased UV doses received were responsible for the increase in malignant melanoma in those sites. Malignant melanoma incidence in the face was independent of sex (Figs. 49 and 50) which rules out identification of the other postulated carcinogen as solar radiation.

12. Malignant melanomas were typically found in members of the professional and managerial classes, whereas other skin cancers were typically found in semi-skilled and skilled workers. This particular finding is inconsistent with the hypothesis that lifetime UV dose is associated with malignant melanoma but may be consistent with an acute UV dose hypothesis.

13. Many carcinogenic agents other than solar radiation have been identified or suspected in the etiology of squamous and basal cell carcinomas. However, the great majority of cases appear to be sun-related, particularly for squamous cell carcinomas.

14. Analysis of the data indicates that urbanization is an important factor in the etiology of basal cell carcinoma. It appears to be about as significant a factor as solar radiation in northern U.S. cities.

15. There is recent evidence in Finland (Table 14), Norway, Denmark, and Warsaw that urbanization is a factor in the etiology of malignant melanoma.

16. The three categories of malignant melanoma, i.e., lentigo-maligna, superficial spreading, and nodular, appear to have characteristics (anatomic site distribution, tumor development time, median age) which can be made compatible with a two- or three-carcinogen theory for the etiology of malignant melanoma.

17. The etiology of malignant melanoma is in a chaotic state. Recently published articles suggest the possibility that virus-like particles and diet (poly-unsaturated foods) may be implicated in the etiology of malignant melanoma.

18. The data for malignant melanoma incidence in Geneva, Switzerland and Zaragoza, Spain should be further examined for possible etiological clues: Geneva has had an anomalously high male/female sex ratio (2.2) and Zaragoza has had extremely low incidence values for both males and females.

19. The biological amplification factor for other skin cancer is equal to or greater than unity but it is unlikely that it exceeds a value of 2. Determination of this factor is a complex multi-dimensional problem and the development of a dose-response model free of uncertainty and controversy is an almost hopeless proposition at the present time.

20. A personal integrating UV dosimeter should be developed to determine the UV dose received by various populations in order to narrow the uncertainty in the determination of the biological amplification factor.

21. A comparison of comprehensive other skin cancer incidence data obtained in a cooperative short-term survey with comprehensive incidence data obtained in a cancer registry is given in Appendix A. It is argued that the use of survey incidence data is likely to lead to spuriously inflated incidence values because of the added diligence in diagnosis by cooperating physicians and the possible cooperation of residents who hear about the government survey and patriotically respond, thus receiving a diagnosis earlier than they otherwise would have received.

22. The acute ultraviolet dose hypothesis for malignant melanoma is in need of further investigation. Sunburn data for various populations and melanoma cases by anatomic site will be essential.

1. INTRODUCTION

This report tests the linkage between skin cancer incidence in white populations and solar ultraviolet radiation on an international basis. The strong linkage of UV radiation to squamous cell carcinoma and basal cell carcinoma is today widely accepted, although there are non-solar-related cases for both types of tumors. Indeed, the cumulative evidence presented throughout this report is so strong for this linkage that it is used at the outset as one of many tools to test the hypothesis that solar ultraviolet radiation is also linked to malignant melanoma: If population group A registers a higher incidence of other skin cancer (basal plus squamous) than population group B, then A must be receiving a higher UV dose than B and, ipso facto, one would expect A to also register a higher incidence of malignant melanoma than B.

Squamous and basal cell carcinomas are discussed separately wherever possible, but the lack of separation of these common tumors as reported to the International Agency for Research on Cancer (IARC) and elsewhere forces usage of the combined classification "other skin cancer." Similarly, malignant melanoma of the skin is reported to the IARC with no breakdown into the three types of malignant melanomas: lentigo-maligna, superficial spreading, and nodular. Consequently, international comparisons of malignant melanoma incidence are perforce limited to the combined classification.

Throughout this paper the hypothesis is tested that an increase in solar ultraviolet radiation is associated with an increase in the incidence of the various types of skin cancer

tumors. Nature fortunately provides us with an imperfect but nonetheless very useful tool by varying solar ultraviolet radiation with latitude. Maximum advantage of this variation is obtained when the incidence in a region of low solar insolation, e.g., Finland, is compared to the incidence in a region of high solar insolation, e.g., southern Texas. Implicit in such a comparison is the reasonable assumption that the chronic ultraviolet radiation dose received by residents of Finland is considerably less than that received by residents of Texas. It would also seem reasonable to expect the number of acute ultraviolet radiation doses per 100,000 population per year to be smaller in Finland than Texas, since the number of calendar days in which the possibility of receiving an acute dose is much smaller and the number of sun exposure hours required on any such day is much higher in Finland. While it could be postulated that a small fraction of the Finnish population take two-week vacations basking in the sun on Mediterranean beaches, it would seem unreasonable to expect that the number of acute doses suffered by such a group could exceed that suffered by the large fraction of southern Texas residents who remain at home throughout the year. Hard data to support these assumptions, however, unfortunately are not available.

In 1952, V. J. McGovern was the first to link malignant melanoma with solar radiation, calling attention to the preponderance of melanomas on the exposed parts of the body (V. J. McGovern, 1952). In 1977, addressing the question of the worldwide increase in malignant melanoma incidence, McGovern ended his article (V. J. McGovern, 1977) with the statement: "This increase in incidence must be an environmental effect, the most likely cause being greater dosage of ultraviolet light both by direct exposure and also by the increasing use of clothing that is permeable to ultraviolet radiation." In the intervening quarter century, scores of articles have been published in which the hypothesis strongly linking ultraviolet radiation to malignant

melanoma has been accepted without serious challenge, although endogenous and other factors were also recognized to play a role in the etiology. Certain paradoxes found in the hypothesis were identified and some ingenious explanations suggested in an attempt to partially resolve them. In this paper it is found that when tested on an international basis, the hypothesis that solar ultraviolet radiation is significantly linked to the etiology of malignant melanoma has so many serious anomalies of various kinds that the probability of such a linkage is all but nil. An alternative hypothesis is proposed in Sections 5 and 6 which involves at least two carcinogenic agents, neither of which is sun-related.

An attempt is made in this report to arrange the pertinent data in systematic form. Thus, descriptions of skin cancer tumors and international geographic variations of skin cancer incidence are discussed in Section 2, time variations in Section 3, age variations in Section 4, and anatomic site variations in Section 5. Other skin cancer (squamous cell and basal cell) and malignant melanoma data are compared in each section. The etiology of skin cancer tumors is discussed in Section 6, and the modelling of other skin cancer incidence with ultraviolet radiation dose is discussed in Section 7.

Incidence rates for other skin cancer incidence for most countries are, in general, unreliable and in some cases not even available. The primary reason for this situation is the lack of adequate reporting of cases of basal cell carcinomas. To reduce the severity of this problem, only data from cancer registries which monitor incidence on a continuous basis is used. However, much survey data is useful for ratio information, i.e., male/female or basal/squamous carcinoma ratios, anatomic site frequencies, etc. Malignant melanoma incidence rates are relatively reliable since the seriousness of the tumor usually involves treating the patient at a hospital where good records are normally kept. It should be emphasized that

most other skin cancer incidence rates, even though reported by a cancer registry, are of dubious accuracy and represent only lower-bound values.

In Appendix A a comparison is made of comprehensive skin cancer incidence data as obtained in a cooperative short-term survey and in a long-term cancer registry. A simple model is devised to illustrate the spurious increase in incidence that could be expected from the survey as a result of possible added diligence in diagnosis by physicians and cooperation from residents.

2. GEOGRAPHIC VARIATIONS

2.1 BASAL CELL AND SQUAMOUS CELL CARCINOMA

The most common skin cancer in Caucasian populations is basal cell carcinoma, a malignant tumor arising from the epidermis (Lever 1967) or its appendages (Sanderson 1968). The tumor is usually found in hair-bearing* skin (Lever 1967), grows slowly by locally invading, but rarely metastasizes (Urbach 1975). Its potential for localized destructiveness and its tendency to recur after therapy are well known (Popkin 1976). In general, 5-year cure rates of 95 percent or better can be expected when treatment is performed by X-ray therapy, surgical excision, or sharp curettage and electrodesiccation by experienced therapists (Popkin 1976).

The incidence of basal cell carcinoma is unavailable for nearly all countries of the world. The Swedish Cancer Registry specifically excludes basal cell carcinomas of the skin in the incidence values for the classification excluding malignant melanoma of the skin or "other skin cancer" in its report to the International Agency for Research on Cancer (Erickson 1976). The Israel Cancer Registry discontinued registration of both squamous cell and basal cell carcinomas in 1967 (Steinitz 1976). Most of the cancer registries in the world lump basal cell and squamous cell carcinomas in the "other skin cancer" classification.

The second most common skin cancer in Caucasian populations is squamous cell carcinoma, a relatively slow-growing tumor

*Excludes only the mucosa or vermilion of the lip, palms of the hand, and soles of the feet.

composed of masses of epidermal cells that tend to form keratin (Urbach 1975). Lymph node metastases from squamous cell carcinoma have been reported with an incidence varying from 0.1 percent to more than 50 percent (Grier 1976). According to Grier (1976) "low rates are reported by dermatologists who usually treat small early lesions, by surveys which include office-treated cases, and by surveys which include all sites. High rates are found in older articles because of late diagnosis, in reports from specialized institutions where advanced cases are treated, and especially in studies in which only certain sites are considered." Mohs recently reported a five-year cure rate of 93.2 percent in 1562 determinate cases (Mohs 1970). In Texas, where there is a high incidence of solar-induced skin cancer, a five-year cure rate of 97.3 percent was reported in 368 cases of squamous cell carcinoma (Freeman and Knox 1967).

The incidence of squamous cell carcinoma is not much better known worldwide than is the incidence of basal cell carcinoma. Inasmuch as the incidence information that is available worldwide is for "other skin cancer," we are unfortunately forced to adopt this classification if we are to compare incidence rates on an international basis. Squamous cell carcinoma and basal cell carcinoma are different tumors with different etiologies and with different responses to ultraviolet radiation. Ideally, the variation in the incidence of these tumors should be studied separately.

An international comparison of skin cancer incidence rates must be based on a common distribution of population by age group. Such a rate, called an age-standardized rate, is the calculated rate that would have occurred if the observed age-specific rates had operated in a standard population, with some arbitrary proportion of people in each age-group. The International Agency for Research on Cancer uses the standard populations of Table 1 for its calculations of African, World, and European age-standardized incidence rates (Doll 1976). The

TABLE 1. STANDARD POPULATIONS USED FOR THE COMPUTATION OF AGE-STANDARDIZED INCIDENCE RATES

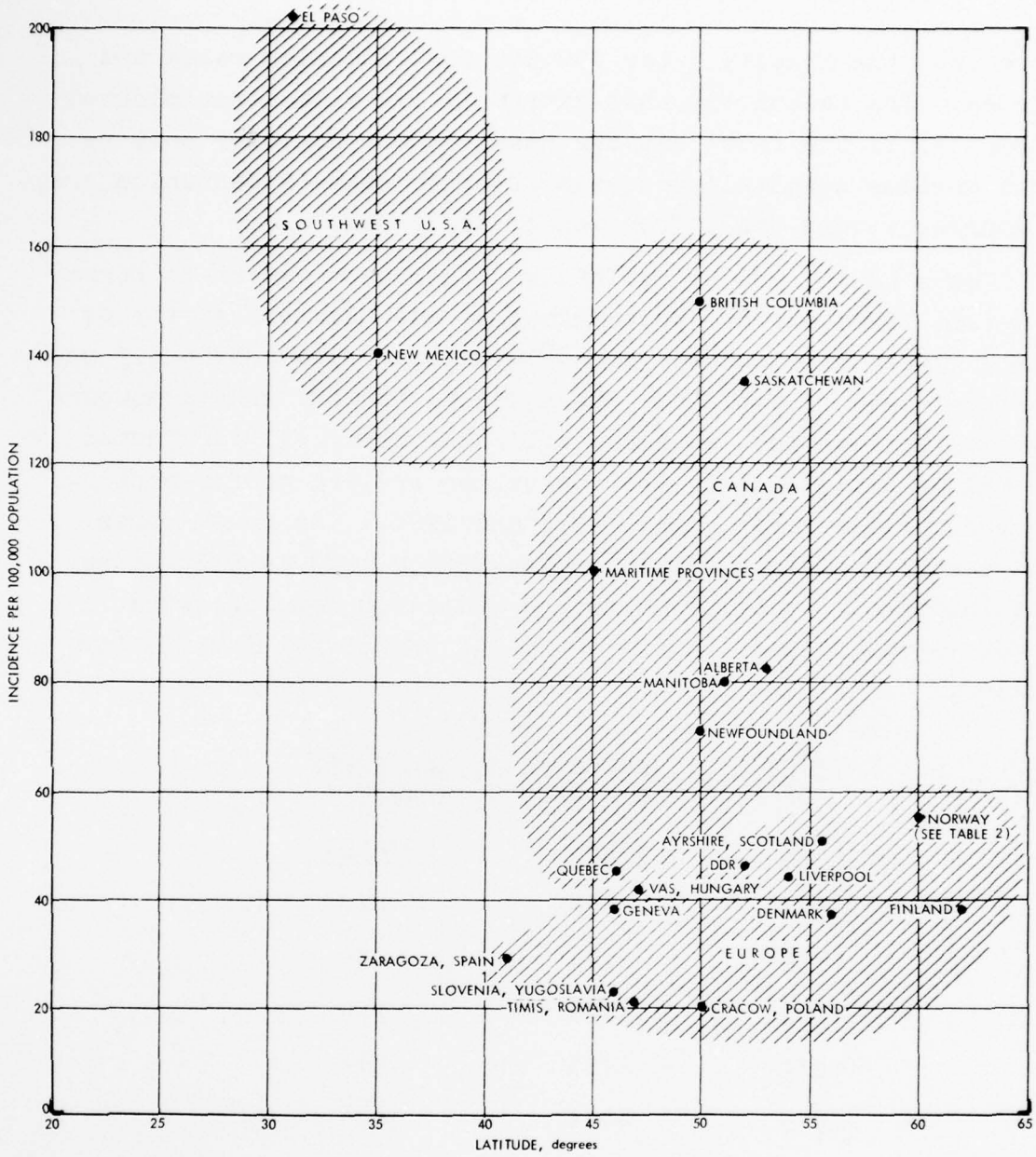
Age (in years)	African	World	European
0-	2,000	2,400	1,600
1- 4	8,000	9,600	6,400
5- 9	10,000	10,000	7,000
10-14	10,000	9,000	7,000
15-19	10,000	9,000	7,000
20-24	10,000	8,000	7,000
25-29	10,000	8,000	7,000
30-34	10,000	6,000	7,000
35-39	10,000	6,000	7,000
40-44	5,000	6,000	7,000
45-49	5,000	6,000	7,000
50-54	3,000	5,000	7,000
55-59	2,000	4,000	6,000
60-64	2,000	4,000	5,000
65-69	1,000	3,000	4,000
70-74	1,000	2,000	3,000
75-79	500	1,000	2,000
80-84	300	500	1,000
85 and over	200	500	1,000
Total	100,000	100,000	100,000

Source: Based on R. Doll, et al., *Cancer Incidence in Five Continents, Volume III,* 1976

African age-standardized incidence rate is completely inappropriate for a study of skin cancer incidence in Caucasian populations. The frequently used world age-standardized incidence rate is also inappropriate since the younger age groups are weighted too heavily, and the older age groups, amongst which the bulk of skin cancer cases are to be found, are weighted too lightly. These effects reflect the inclusion of the high birth rates and high death rates that are prevalent in the underdeveloped nations of the world. The European age-standardized incidence rate is therefore adopted in this paper as most appropriate to compare skin cancer incidence rates in predominantly Caucasian countries.

In Fig. 1 are plotted the European age-standardized incidence rates for other skin cancer in white males as a function of latitude in various regions of Europe and North America as reported by cancer registries to the International Agency for Research on Cancer (Waterhouse et al., 1976). Note that the reporting sites in Europe, Canada, and Southwest U.S.A. fall in three separate regions, with a distinct latitude gradient from Scandinavia to El Paso, Texas. The large scatter between latitudes 45° and 55° (British Columbia has triple the other skin cancer incidence of Quebec) probably arises because of large differences in the following: (1) ethnic composition; e.g., 70 percent of the population of the provice of Quebec is of French extraction (Fredette 1976) whereas people of British extraction predominate in the other provinces, (2) climate; e.g., coastal British Columbia residents enjoy the most frequently mild climate in Canada, (3) occupations; e.g., Saskatchewan is mainly an Agricultural province (Barclay 1976), (4) leisure activities; and (5) under-reporting of cases, particularly of basal cell carcinomas.

Hawaii, at a latitude of 21° N, is the site closest to the equator for which incidence data from a cancer registry is available for a Caucasian population. It would therefore be expected to report the highest incidence of other skin cancer, but instead



Source: Waterhouse, J., Muir, C., Correa, P. and Powell, Jean, eds., "Cancer Incidence in Five Continents, Volume III", Lyon, (IARC Scientific Publications No. 15) 1976.

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FIGURE 1. Other skin cancer, age-standardized incidence for white males

it reports the lowest, 3 per 100,000 for Caucasian males and females. The reason for this extremely low value (not plotted in Fig. 1) is the fact that the Hawaii Tumor Registry only reports serious hospitalized cases of other skin cancer which are, of course, a very small fraction of the total.*

There was no report to IARC on other skin cancer in Norway (Pedersen 1976) but Dr. Knut Magnus of the Cancer Registry of Norway kindly released the recently acquired and previously unpublished data of Table 2. These values for the annual number of cases include both squamous cell and basal cell carcinomas. Dr. Magnus believes that the low values reflect poor reporting for the earlier years, i.e., 1971 and 1972. The crude other skin cancer incidence rates for the period 1973-1975 in Norway (population of 2 million males and 2 million females) were approximately 55 per 100,000 for males and 50 per 100,000 for females.

TABLE 2†. NUMBER OF ANNUAL CASES OF OTHER SKIN CANCER IN NORWAY

YEAR	MALES	FEMALES
1971	636	573
1972	946	835
1973	1073	950
1974	1153	1046
1975	1004	1008

†Personal Communication with Dr. Knut Magnus, Cancer Registry of Norway, November, 1977.

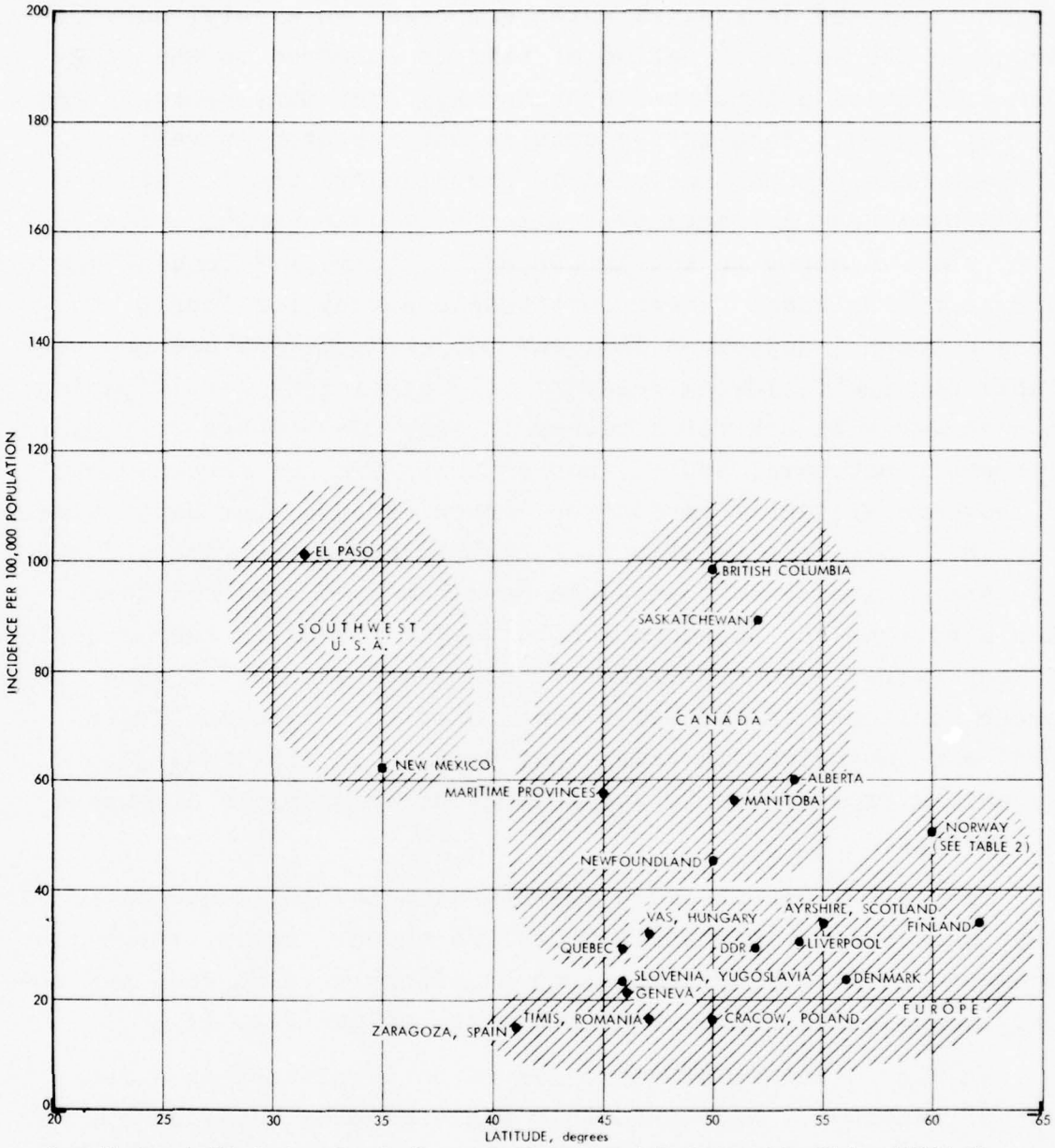
*Telephone conversation with G. Bratten, Hawaii Tumor Registry, April, 1978.

It should be pointed out that many other sources of skin cancer incidence data exist which are based on special surveys conducted over a short period of time as compared to the long-term statistics accumulated continuously over many years by cancer registries. Such survey data is not accepted as valid by IARC and hence is not included in Fig. 1 where the incidence values have been averaged over a 3- or 4- year period circa 1970. As explained to the author by Dr. C. Muir,* special surveys such as the National Cancer Institute's survey for four U. S. areas between 1 September 1971 and 29 February 1972 are not reliable for the following reasons: (1) physicians participating in a survey will ask for a biopsy in many cases where they otherwise would not have, and (2) nonresidents are not screened out as they are by cancer registries. Both effects, but particularly the first, may lead to significantly higher survey values for skin cancer incidence than would have been the case had there been a routine but thorough monitoring of the cases over a period of many years. The Dallas-Fort Worth (latitude 32.8°) other skin cancer incidence in the NCI 6-month survey (Urbach and Scotto, 1975) was approximately twice that of El Paso (latitude 31.5°). A possible explanation for this large discrepancy is discussed in Appendix A.

In Fig. 2, the European age-standardized incidence rates for other skin cancer in white females are shown. Again, there is apparent a latitude gradient from Scandinavia to El Paso but one that is obviously weaker than for white males (Fig. 1).

In Fig. 3 the male/female sex ratio is plotted as a function of latitude. Note that this ratio exceeds unity at all sites, and that it has a latitude gradient, increasing from close to unity in Finland and Norway to two in El Paso. From this behavior in the sex ratio it can be deduced that, in general, males expose themselves to sunlight more in relation to females, with the exposure ratio increasing with decreasing latitude.

*Chief, Unit of Epidemiology and Statistics, IARC, Lyon, France.



Source: Waterhouse, J., Muir, C., Correa, P. and Powell, Jean, eds., "Cancer Incidence in Five Continents, Volume III", Lyon, (IARC Scientific Publications No. 15) 1976.

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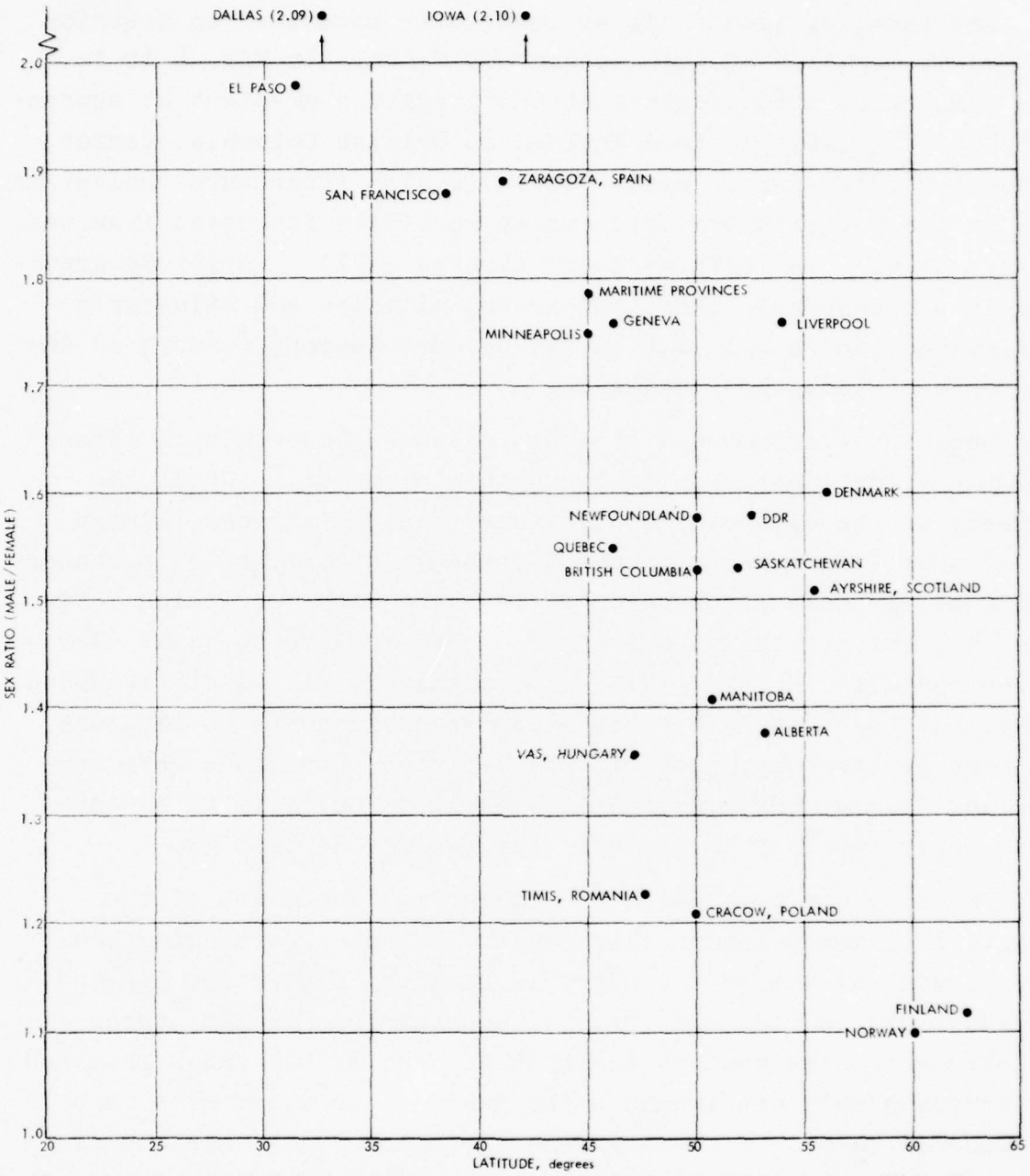
FIGURE 2. Other skin cancer, age-standardized incidence for white females.



Sources: Waterhouse, J., Muir, C., Correa, P. and Powell, Jean, eds., "Cancer Incidence in Five Continents, Volume III", Lyon, (IARC Scientific Publications No. 15) 1976, and Urbach and Scotto, 1975.

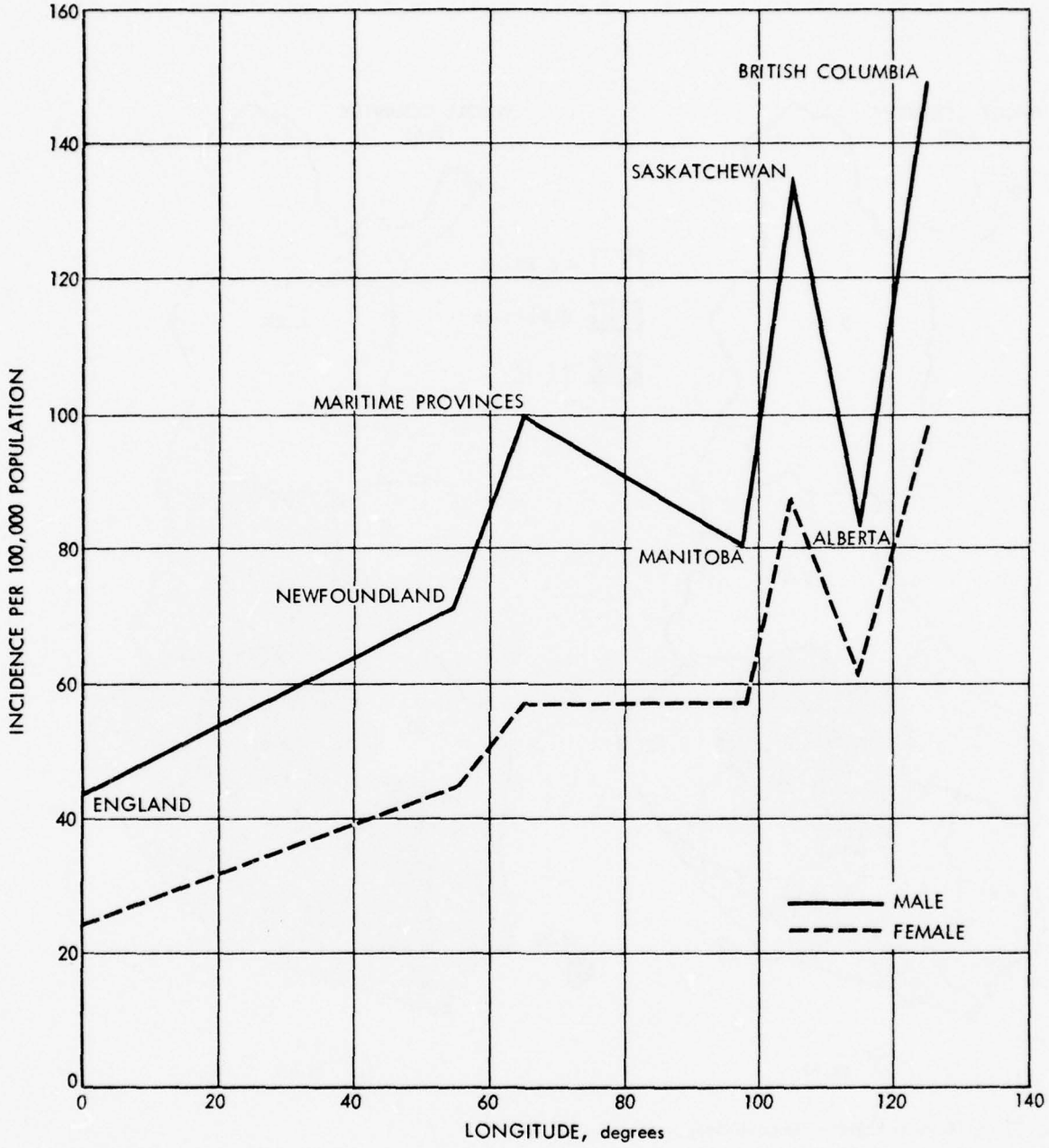
FIGURE 3. Sex ratio for other skin cancer incidence.

Latitude, by itself, is an inadequate parameter to describe the global behavior of skin cancer incidence. In Fig. 4 it is seen that there also exists a strong longitude gradient at approximately 50° N latitude from England to British Columbia, Canada, increasing from east to west. There is also literature indicating that in the Soviet Union skin cancer morbidity increases from west to east as well as north to south (Dancig 1977). Longitude gradients in stratospheric ozone thickness, climatic and life-style differences, and air pollution may be contributory factors in the existence of longitude gradients.

Many surveys in the literature discuss geographic incidence variations for other skin cancer within a country. While the accuracy of the data can be questioned in some surveys, almost all of them lend support to the hypothesis that other skin cancer incidence for Caucasians tends to increase with decreasing latitude and, inferentially, with increasing exposure to solar ultraviolet radiation. This qualitative conclusion is widely accepted today, but the quantitative behavior of incidence with latitude or, more pertinently, with ultraviolet dose, remains a very complex and highly controversial area which is unlikely to be satisfactorily resolved in the near future (see Section 7).

Probably the most complete and recent tabulation of the variation of non-melanoma skin cancer incidence, excluding basal cell carcinoma, within a country is shown by region for Finalnd for 1961-1973 in Fig. 5.* Dr. L. Teppo of the Finnish Cancer Registry estimates that at least 95 percent of the cases reported are squamous cell carcinomas. The latitude gradient here is only obvious for males, if the low female rate of 0.8 in Lapland is disregarded. The highest incidence for males (5.2) and females (3.8) was registered in the near central province of Kuopio, again illustrating the importance of factors other than latitude in the epidemiology.

*Finnish Cancer Registry, unpublished



Source: Waterhouse, J., Muir, C., Correa, P. and Powell, Jean, eds., "Cancer Incidence in Five Continents, Volume III, Lyon, (IARC Scientific Publications No. 15) 1976.

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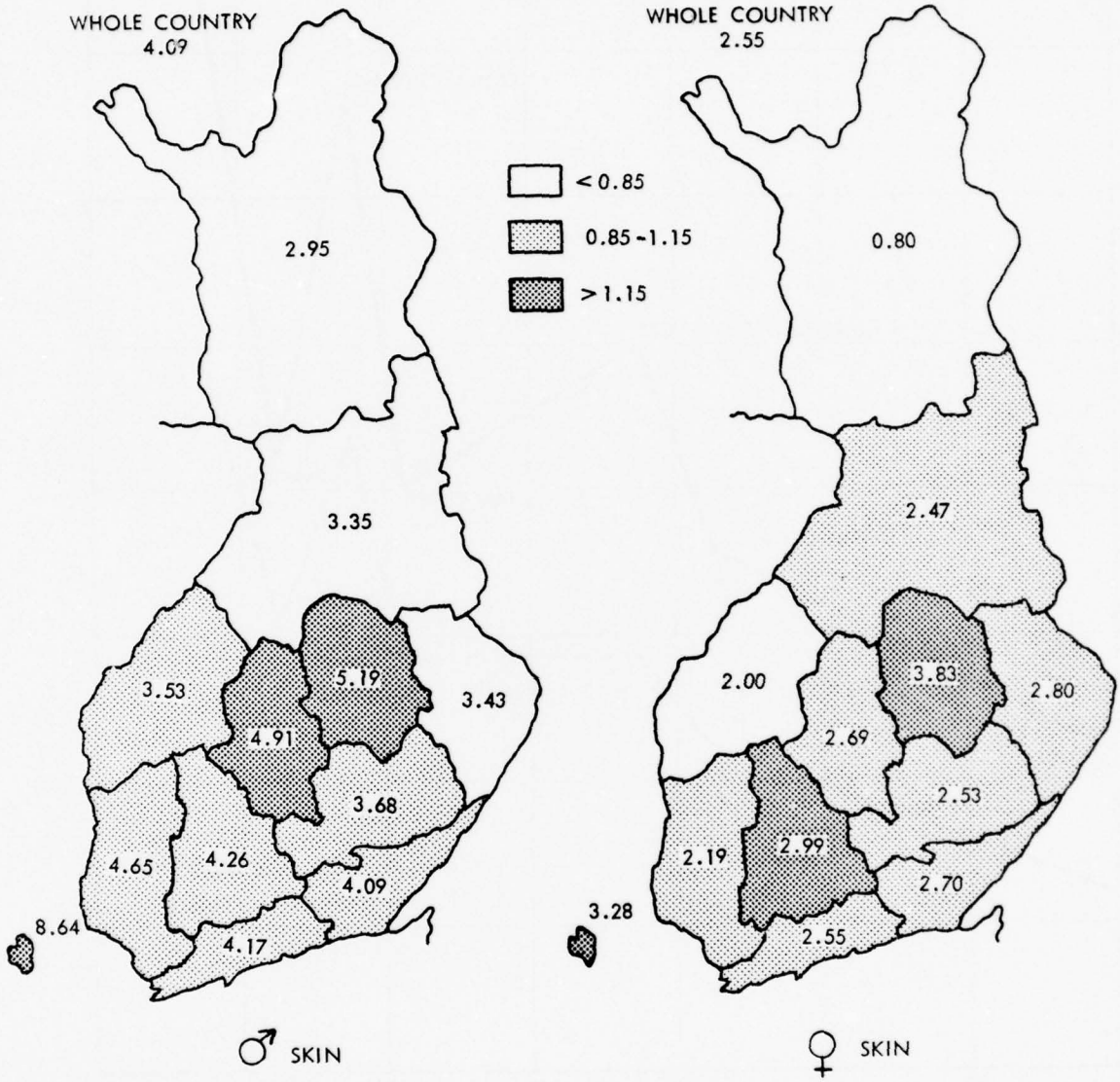
FIGURE 4. Other skin cancer, age-standardized incidence at approximately 50° N latitude



Source: Finnish Cancer Registry, Unpublished.

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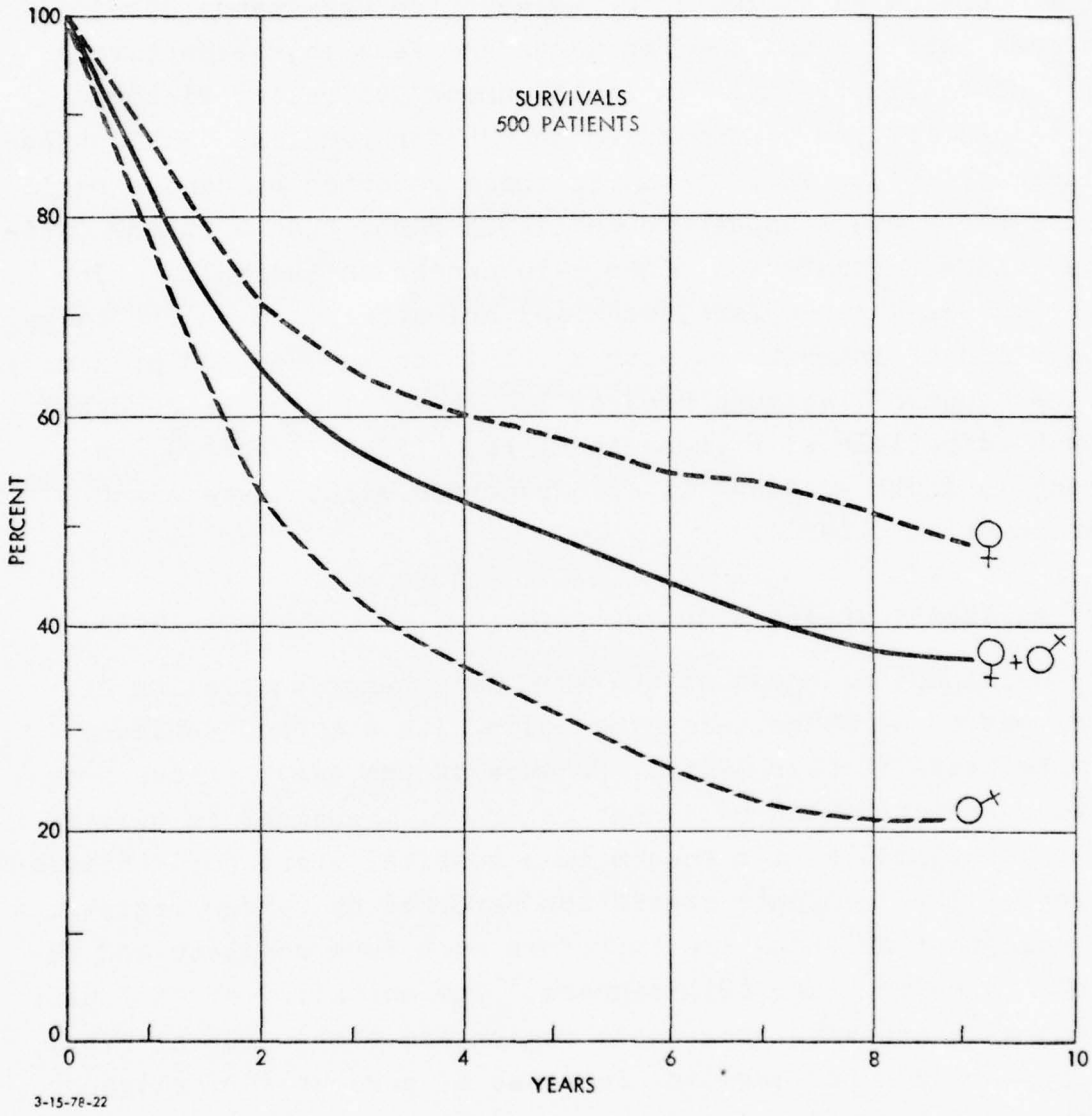
FIGURE 5. Non-melanoma skin cancer incidence, excluding basal cell carcinoma in Finland; mean annual age-adjusted incidence rates in 1961-1973 by sex and province. The stratification indicates relative rates (whole country = 1.00).

The highest incidence of other skin cancer in the world can be expected to be found in Queensland in northernmost Australia, where "considered estimates of values" for age-standardized incidences were 265 and 156 for males and females, respectively (Gordon, et al., 1972). In southernmost Australia, Victoria, the values fell to 67 for males and 39 for females. While these values may not be as reliable as those reported by cancer registries, there would appear to be little doubt that a strong latitude gradient exists for other skin cancer in Australia. The high incidence rates for Queensland are attributed to the large proportion of inhabitants with a Celtic background and proximity to the equator (latitude band of 17^{o}-28^{o}). The rates reported appear compatible with those in El Paso (Figs. 1 and 2). A strong latitude gradient is also reported within Queensland (Gordon et al., 1972).

2.2 MALIGNANT MELANOMA OF THE SKIN

Malignant melanoma of the skin is a tumor consisting of black masses of melanin-forming cells with a marked tendency to metastasis (Urbach 1975). Because of the very serious prognosis associated with malignant melanoma, treatment in Western countries almost always occurs in a hospital where documentation is good. The incidence statistics reported by cancer registries for malignant melanoma are therefore much more complete and reliable than for other skin cancers. The mortality of malignant melanoma varies with geographic region and time. In the U.S., the 5-year adjusted survival rate was 67 percent for malignant melanoma patients diagnosed between 1965 and 1969 (End Results in Cancer, National Cancer Institute, 1972). A study of 500 patients with melanoma of the skin at the Radium Centre in Copenhagen, Denmark (Olsen 1967) found a 5-year survival rate of 50 percent, with a 59 percent rate among females and a 31 percent rate among males (Fig. 6). The first patients in this series were treated in 1949 and survival rates for malignant



Source: G. Olsen, 1967

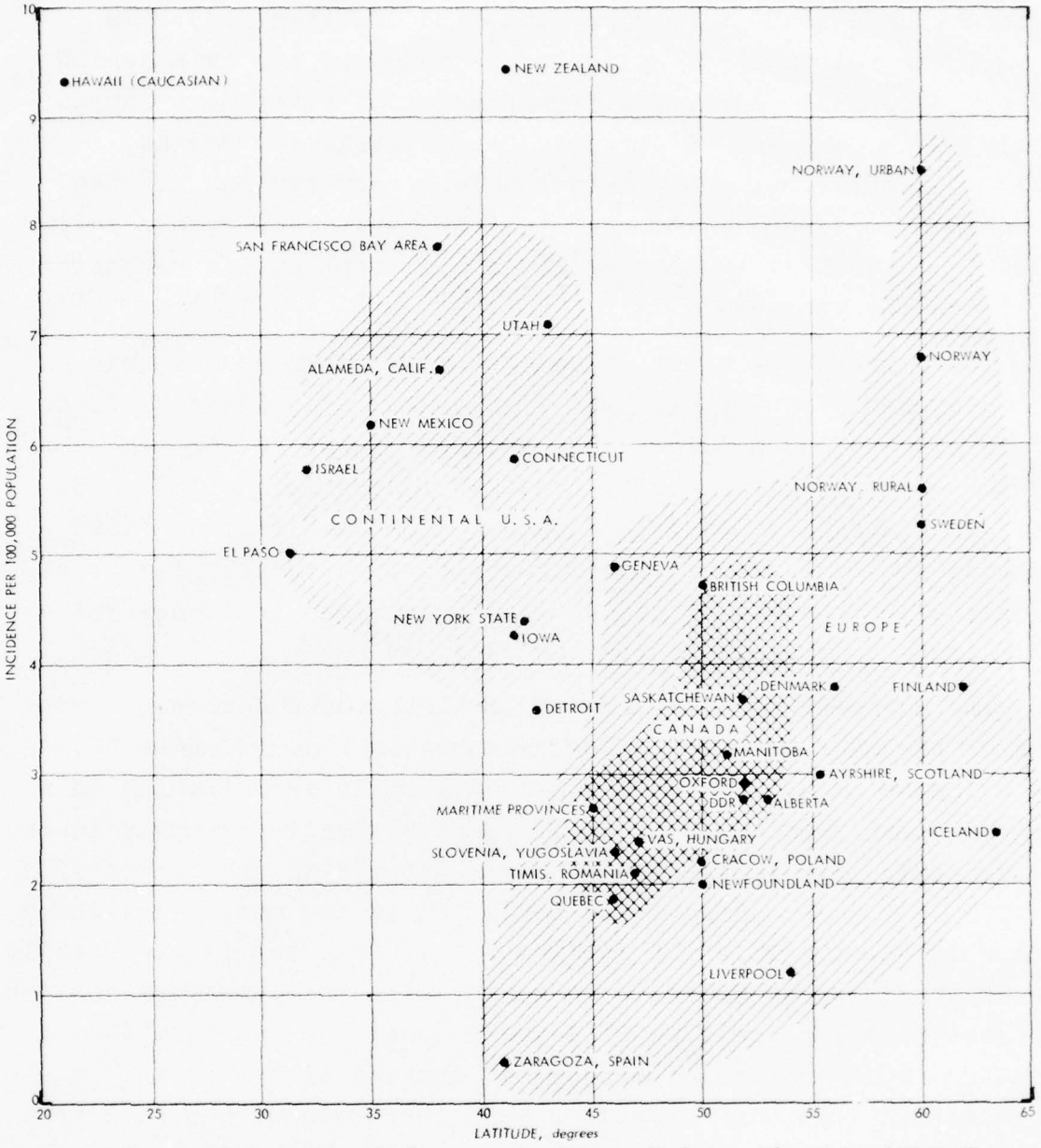
FIGURE 6. Melanoma survival in Denmark

melanomas have been increasing with time (Section 3.3). In Norway, for all cases of malignant melanoma of the skin during the period 1953 to 1971, the 5-year survival rates were approximately 65 percent and 45 percent, respectively (K. Magnus, 1977). Clearly, malignant melanoma is a very serious disease. While it occurs rarely compared to other skin cancer, its incidence is apparently increasing at an alarming rate in Caucasian countries (Section 3).

There are three types of malignant melanoma of the skin with different etiologies: (1) lintigo-maligna, (2) superficial spreading, and (3) nodular, with median ages of 70, 56, and 49 years, respectively (National Academy of Sciences, 1976). However, on a worldwide basis, malignant melanoma incidence data reported to IARC does not distinguish between these three types, necessitating the use of the available combined incidence values for malignant melanoma as was the case for other skin cancer.

The European age-standardized incidence for malignant melanoma of the skin in white males is shown in Fig. 7. Note that the evidence of a latitude gradient for malignant melanoma on an international basis is ambiguous. A most puzzling anomaly is the unexpectedly high incidence shown for Norway* in the period 1968 to 1972. If solar ultraviolet radiation is the most significant factor in the induction of malignant melanoma, how is it possible for urban Norwegian males to have virtually the same incidence as New Zealand males residing 20 degrees closer to the equator and Hawaiian Caucasian males residing 40 degrees closer to the equator? To attribute this high Norwegian male incidence of 8.5 to a very high ethnic susceptibility is unconvincing. Minneapolis-St. Paul, an urban area with a substantial proportion of its population of Norwegian or Swedish extraction, lies 15 degrees closer to the

*For a discussion of the high incidence and mortality of malignant melanoma in Sweden compared to England and Wales, see J.A.H. Lee and H.J. Issenberg, 1972.



Source: Waterhouse, J., Muir, C., Correa, P. and Powell, Jean, eds., "Cancer Incidence in Five Continents, Volume III", Lyon, (IARC Scientific Publications No. 15) 1976.

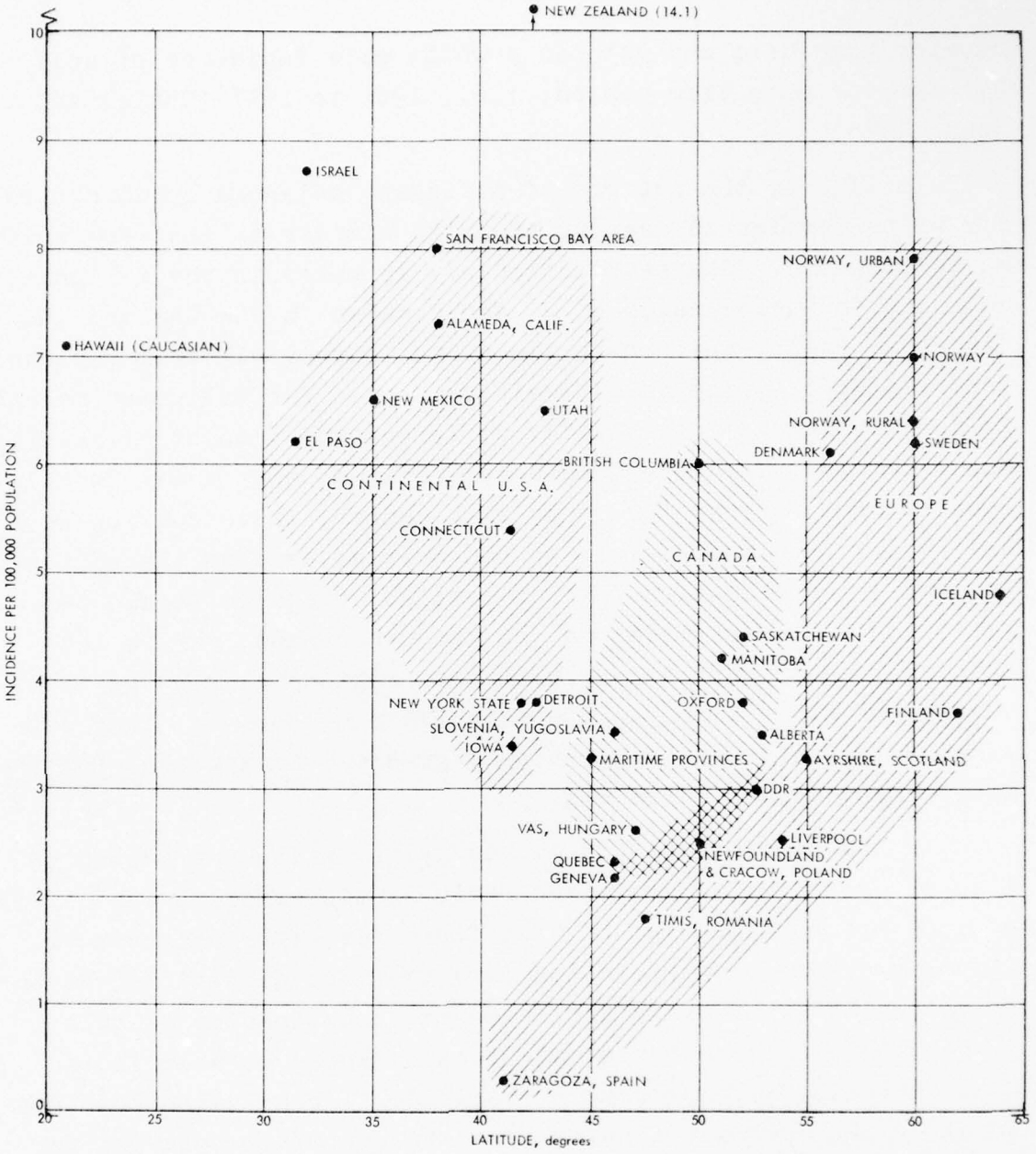
FIGURE 7. Melanoma of skin, white male age-standardized incidence.

equator than Oslo and yet had a white male incidence of only 3.6 for the same time period, i.e., 1969 to 1971 (Cutler and Young 1975).

In Fig. 8, the pattern of malignant melanoma incidence rates for white females is seen to be quite similar to that for white males (Fig. 7). A great discrepancy is noted in the malignant melanoma incidence ratio of 47 for females in New Zealand and Zaragoza, Spain, which both lie approximately 41° from the equator. In Fig. 9, the male/female sex ratio for malignant melanoma is seen to behave in a totally different way from other skin cancer (Fig. 3). The male/female sex ratio exceeds unity in all geographical regions for other skin cancer, in consonance with the observation that males, on the average, expose themselves to more solar radiation than do females; the male/female sex ratio for malignant melanoma, on the other hand, may be less than or greater than unity, with most regions clustering about a value of 0.9. Also, unlike other skin cancer, no clear evidence of an international latitude gradient is apparent for the male/female sex ratio in Fig. 9.

In the continental U.S.A., oddly, a latitude gradient in Fig. 9 for the male/female sex ratio is discernible, but it has a slope of opposite sign to that found for other skin cancer. If solar ultraviolet radiation were the most significant factor in the etiology of malignant melanoma, the behavior of this slope would imply that the male/female exposure ratio in the U.S. decreases with decreasing latitude, a conclusion that contradicts the opposite finding from the sex ratio behavior for the incidence of other skin cancer. In the Canadian provinces, the male/female sex ratio is approximately the same at 0.8.

The exceptionally high male/female sex ratio of 2.2 for malignant melanoma incidence in Geneva (Fig. 9) is an anomaly that has no parallel in its rather ordinary value of 1.76 for other skin cancer (Fig. 3). This anomaly can be traced back to



Source: Waterhouse, J., Muir, C., Correa, P. and Powell, Jean, eds., "Cancer Incidence in Five Continents, Volume III", Lyon, (IARC Scientific Publications No. 15) 1976.

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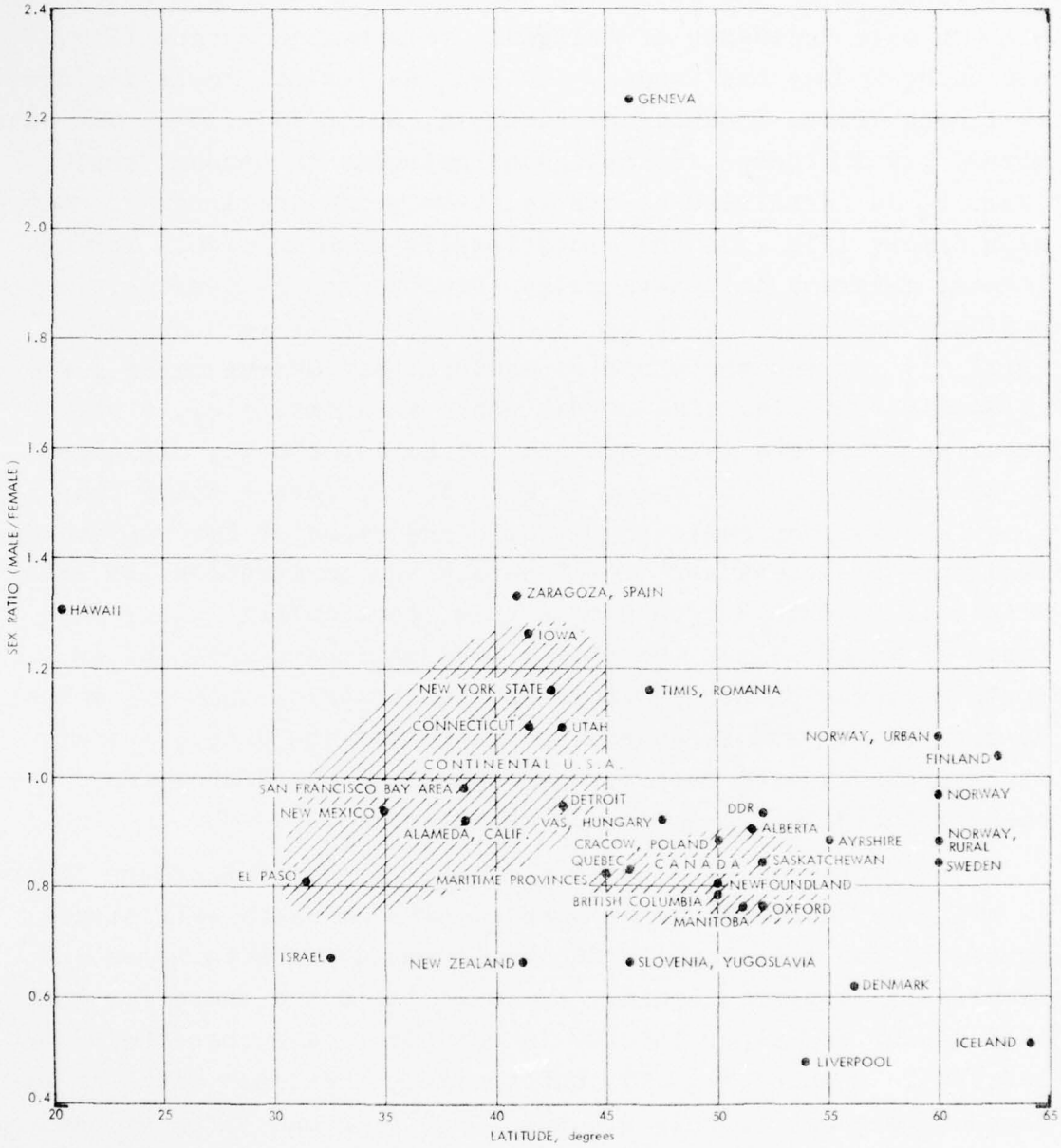
FIGURE 8. Melanoma of skin, white female age-standardized incidence.



Source: Waterhouse, J., Muir, C., Correa, P. and Powell, Jean, eds., "Cancer Incidence in Five Continents, Volume III," Lyon, (IARC Scientific Publications No. 15) 1976.

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FIGURE 9. Sex ratio for incidence of malignant melanoma of skin.

a combination of the following two factors: Geneva has (1) the highest male incidence of malignant melanoma in Europe (Fig. 7) excluding Norway and Sweden, and (2) the lowest female incidence, excluding Timis, Romania and Zaragoza, Spain (Fig. 8). The relatively low incidence for malignant melanoma in Geneva females (Fig. 8) is paralleled by the relatively low incidence of other skin cancer (Fig. 2); the exceptionally high incidence for malignant melanoma in Geneva males (Fig. 7) has no parallel in the ordinary incidence of 38 per 100,000 for other skin cancer (Fig. 1). It can therefore be deduced that Geneva males suffer an anomalously high risk of malignant melanoma, i.e., a risk peculiar to Geneva which can only be satisfactorily explained by postulating the presence of a causative factor other than solar ultraviolet radiation.* While one third of the registered residents of Geneva are "foreigners," the immigration has been mainly from South European countries, particularly Italy and Spain (Raymond 1976). Mortality from malignant melanoma in South European countries, however, is far below that of central Europe (Jensen and Bolander) and therefore the Geneva anomaly would probably have been even stronger had the "foreigners" been excluded in the incidence calculations.

The relative immunity of the populations of Southern Europe to malignant melanoma is another anomaly which is well illustrated by the very low incidences reported for both males and females in Zaragoza, Spain. The male incidence there for other skin cancer of 29 per 100,000 is not much lower than the 45 per 100,000 in Quebec (Fig. 1), but the male incidence rate for malignant melanoma is only 0.4 per 100,000 or one-fifth of the male incidence for Quebec (Fig. 7). In Zaragoza there are more than 200 clear and sunny days a year (Zubiri 1976) and practically all of the 757,435 (1970 census) inhabitants belong to the Mediterranean white race. The province of Quebec has fewer sunny

*Unless presently unavailable data indicate most male melanoma cases occur on the face of skiers.

days than Zaragoza, lies 4 or 5 degrees farther north, and has a population dominated by descendants of the Mediterranean white race. It would appear that an explanation of the very low incidence of malignant melanoma in Spain as well as other Mediterranean countries must include a significant factor(s) other than low ethnic sensitivity to solar ultraviolet radiation.

The greatest anomaly in the geographic variation in the incidence of malignant melanoma, again assuming exposure to solar radiation to be the most significant factor in its causation, is to be found in a comparison of the data for Norway and Zaragoza. From Fig. 7 it can be deduced that if the Norwegian male population had lived all their lives in Zaragoza alongside the Spanish, they would have experienced far more than 20 times (current ratio) the melanoma incidence of Spanish males since Zaragoza's climate is far milder and sunnier than Norway's. There is nothing in the literature of which we are aware to suggest that so great a difference in genetic predisposition to malignant melanoma could exist between two different ethnic groups of the white race. However, small control studies in New York City (Gellin et al., 1969) and Sydney, Australia (Lancaster and Nelson 1957) indicate that there is a tendency for patients with malignant melanoma to have light complexions, light eyes, blond or red hair, and to spend a greater amount of time outdoors than members of the control group. While these studies uncovered significantly increased risks for persons with the aforementioned characteristics, their relative magnitudes (Figs. 10 to 13) indicate a likely variation in the genetic factor of perhaps 2 or 3, certainly not of more than 20. An ancestral study in Australia (Brown et al., 1971) indicated that amongst patients with either malignant melanoma, squamous cell carcinoma, or basal cell carcinoma, the percentage of persons who were half Celtic or over was almost double the figure obtained for controls. Further corroboration of the unlikelihood that the variability in the genetic factor exceeds two can be had by comparing the malignant melanoma incidence rates in Figs. 7 and 8 for geographic regions at approximately the same latitudes but

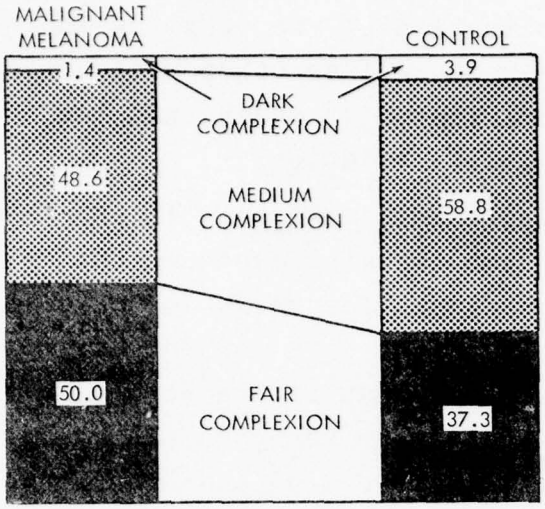

FIGURE 10.
Percentage distribution by complexion

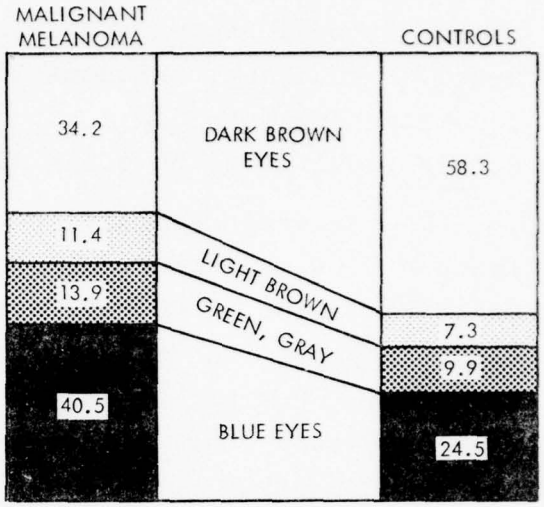

FIGURE 11.
Percentage distribution by color of eyes

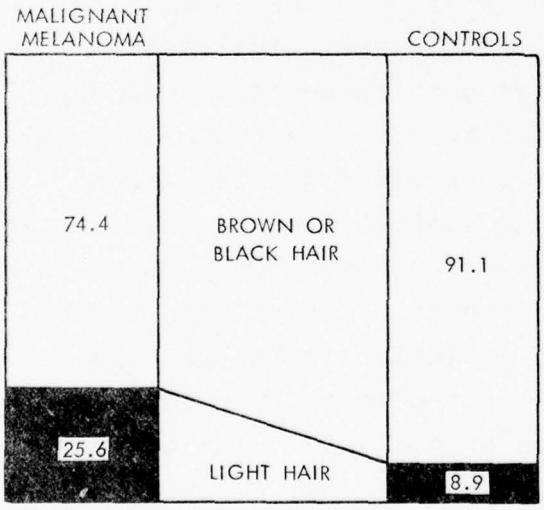

FIGURE 12.
Percentage distribution by color of hair

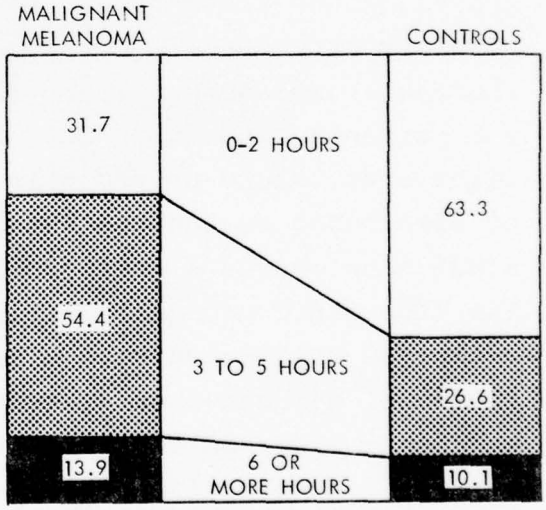

FIGURE 13.
Percentage distribution by estimated daily hours of outdoor activity

Source: Gellin et al., Copyright 1969, American Medical Association.

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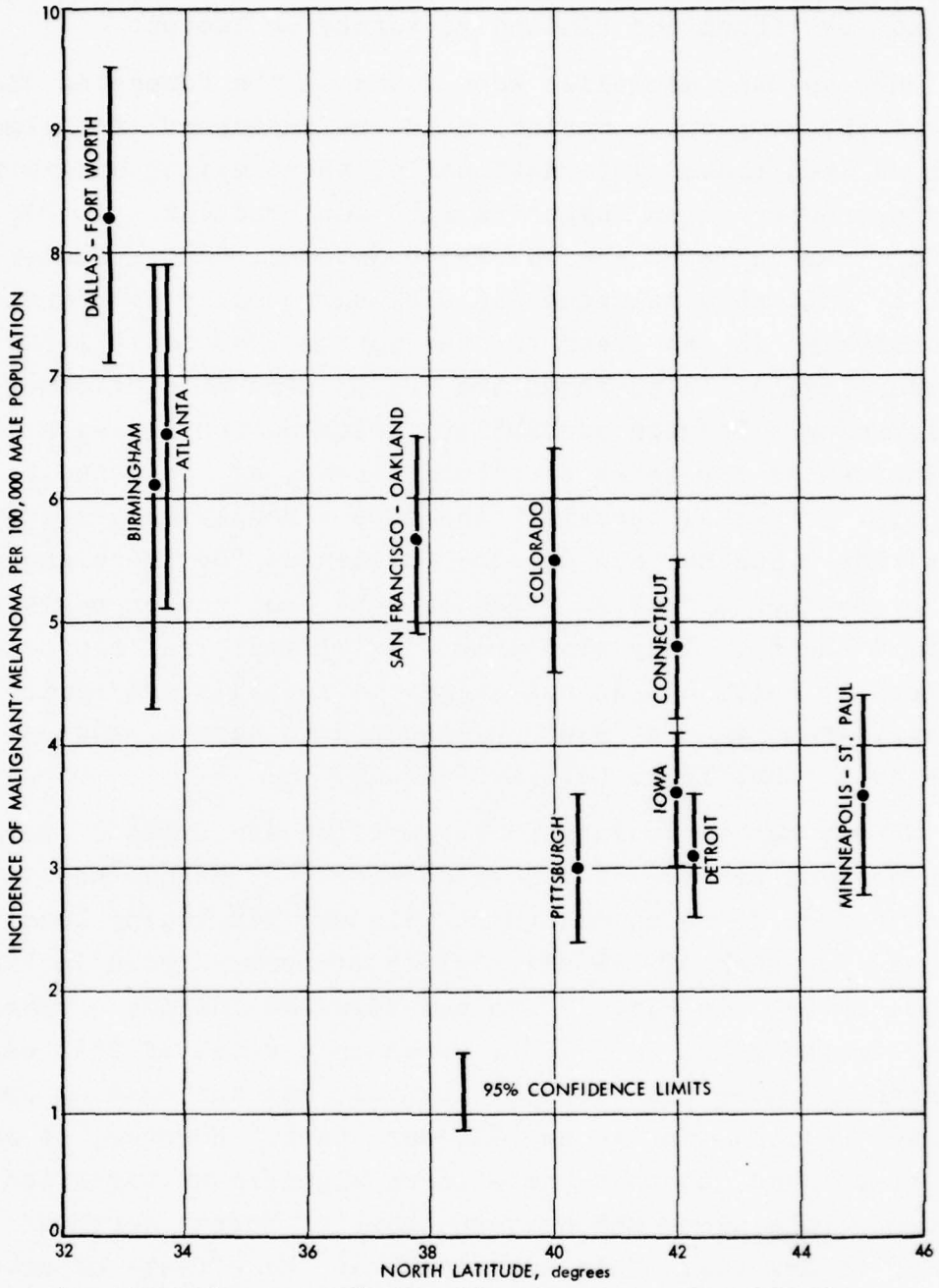
with different ethnic populations, e.g., Quebec vs the other Canadian provinces and Finland vs Norway or Sweden.

Whereas many anomalies were found in the foregoing discussion of the geographic variation in the incidence of malignant melanoma when viewed internationally, there exists data within a given country which suggest a latitude gradient. In Figs. 14 and 15 are plotted the NCI Third National Cancer Survey incidence of malignant melanoma for U.S. white males and females, respectively, in ten areas for the period 1969 to 1971 (Cutler and Young 1975). Also shown are the 95 percent confidence limits assuming a Poisson probability distribution for each area. The incidences for these particular areas, age-adjusted to the 1950 U.S. standard, certainly are more strongly suggestive of a latitude gradient than are the incidences for the eight areas in the continental U.S.A. based on data from cancer registries (Figs. 7 and 8). They also show a male/female sex ratio that is close to unity but do not suggest a latitude gradient, unlike the U.S. group in Fig. 9 which appeared to have a slope of sign opposite to that for other skin cancer.

Norway has a population of 4 million and extends over a latitude band between 58 and 72 degrees. K. Magnus has investigated the incidence of malignant melanoma (excluding lentigo maligna) for each of the six regions of Norway shown in Fig. 16 (Magnus 1975). In Fig. 17 the age-adjusted incidence rates are shown for the years 1955-1970, based on a total of 2541 cases. The highest rates are observed in Oslo, its surrounding counties (Eastern region), and in the Southern part. However, it should also be pointed out that there is no significant variation in incidence rate along the Western coast of Norway north of a latitude of 60 degrees. This suggests that the effects of urbanization may be a significant factor in the etiology of malignant melanoma. The excess incidence rate for urban as compared to rural Norway is also illustrated in Figs. 7 and 8 for the more recent period 1968-1972.



Source: National Cancer Institute "Third National Cancer Survey: Incidence Data", DHEW Publication (NIH) 75-787, 1975.

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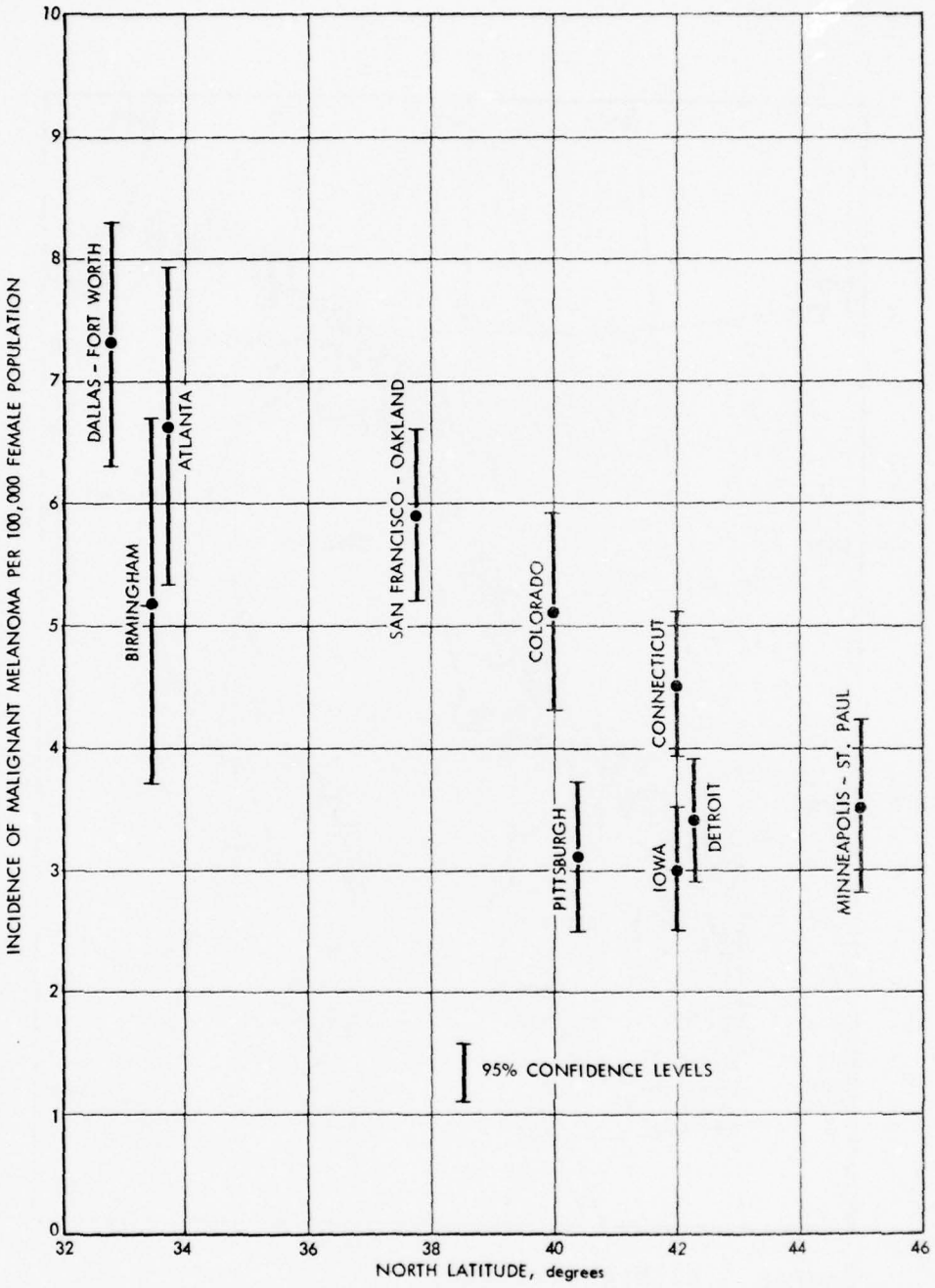
FIGURE 14. Incidence of malignant melanoma for U.S. white male population in 10 areas for the period 1969-1971



Source: National Cancer Institute "Third National Cancer Survey: Incidence Data", DHEW Publication (NIH) 75-787, 1975.

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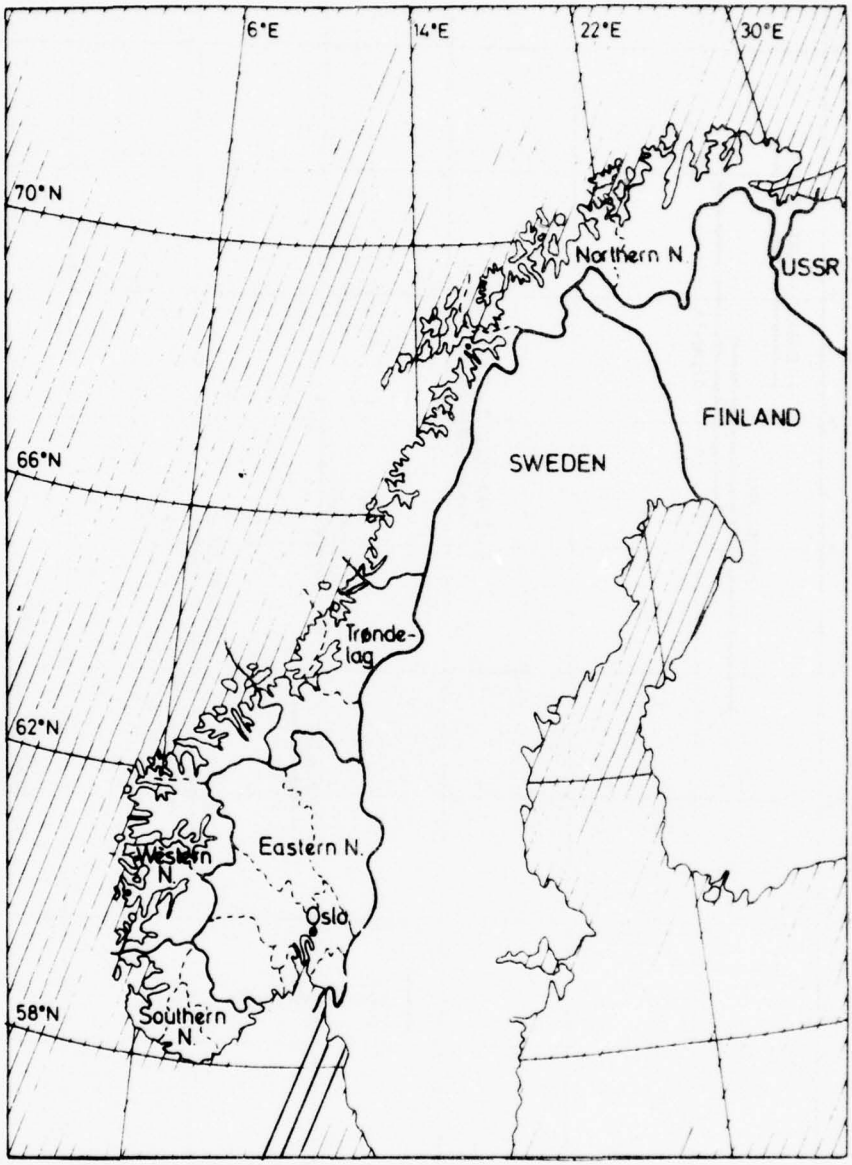
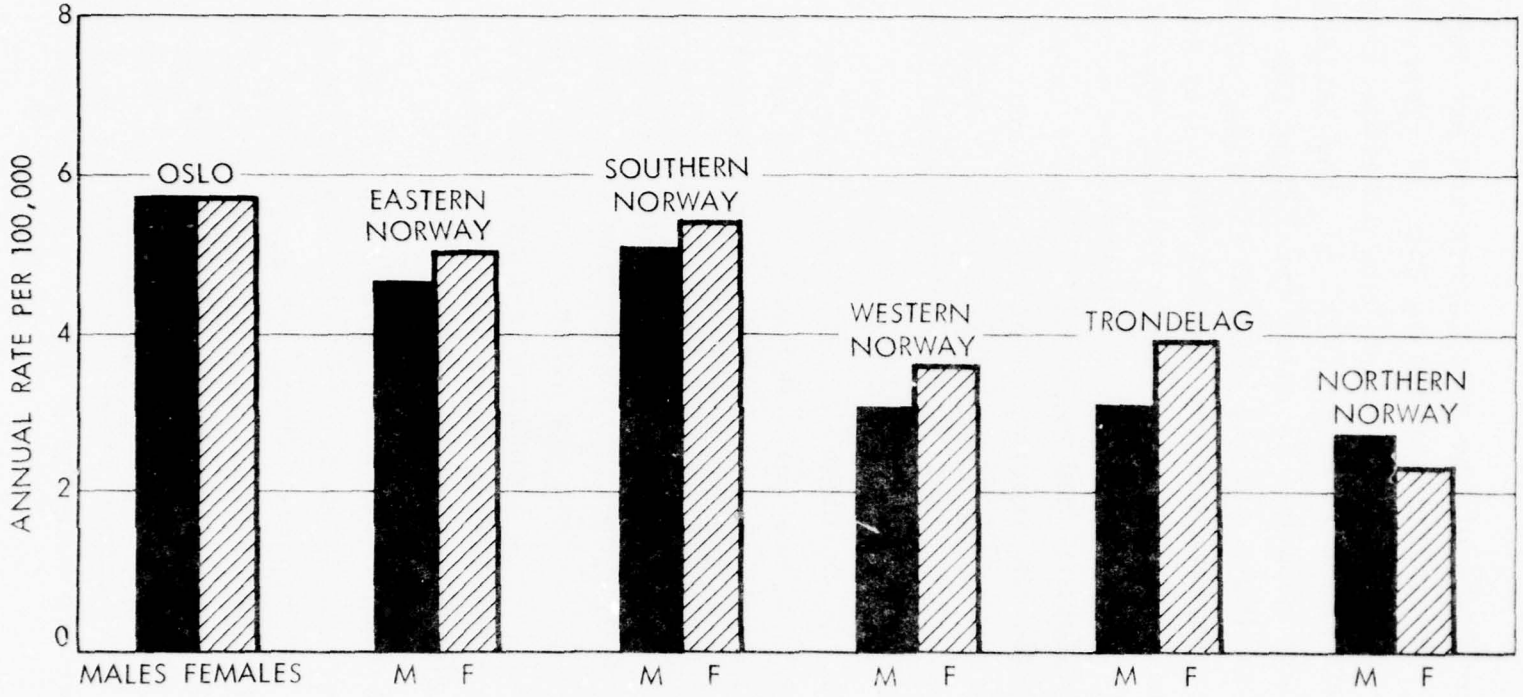
FIGURE 15. Incidence of malignant melanoma for U.S. white female population in 10 areas for the period 1969-1971



Source: K. Magnus, 1975

FIGURE 16. Geographic regions in Norway



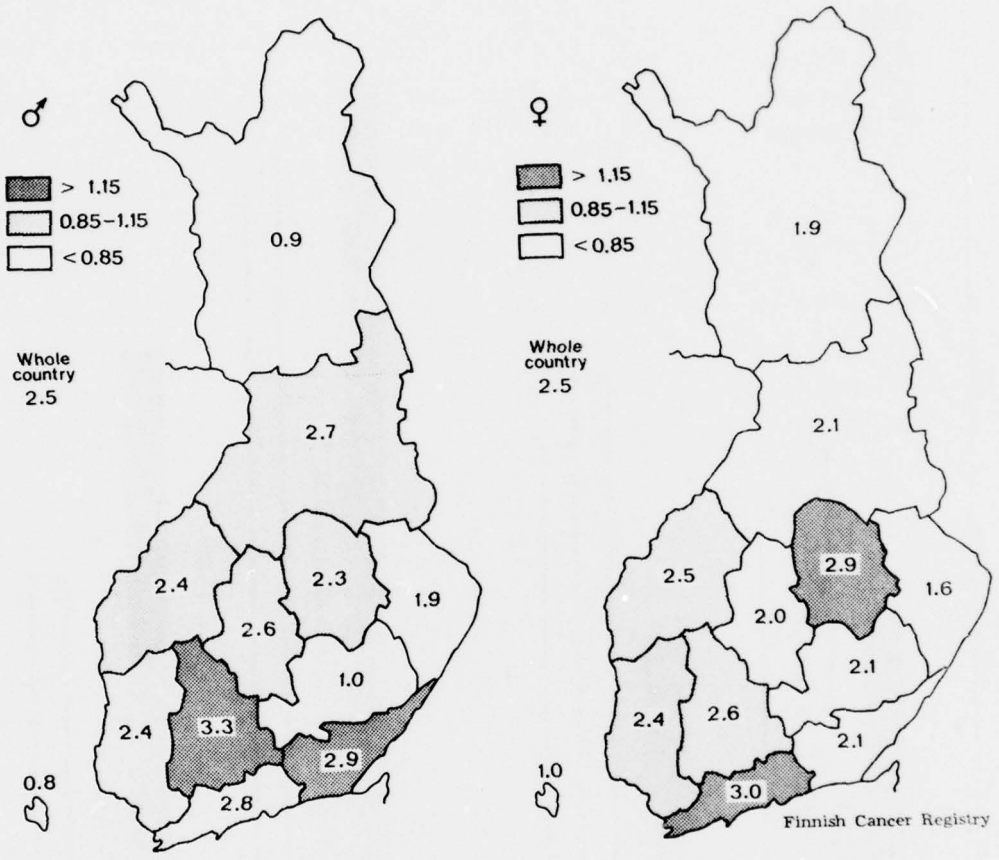
Source: K. Magnus, 1975

FIGURE 17. Total age-adjusted incidence rate of malignant melanoma of skin in Norway 1955-1970 by region

Incidence of melanoma of the skin by sex and province for Finland in 1961 to 1969 is illustrated in Fig. 18 (Teppo et al., 1975). Note that, in contrast to the strong latitude gradient for squamous cell carcinoma in males (Fig. 5), the latitude gradient for malignant melanoma in males (excluding the 0.9 value for Lapland) is weak, and the reverse situation prevails for females. Also note that the two central provinces which had the highest male incidence of squamous cell carcinoma of approximately 5 (Fig. 5), indicating (presumptively) a maximum exposure to solar radiation, had melanoma incidence rates of only approximately 2.5, the average value for Finland. Finally, note that the male/female incidence ratio for the central province of Kuopio is 5.19/3.83 or 1.35 for squamous cell carcinoma and 2.3/2.9 or 0.79 for malignant melanoma.

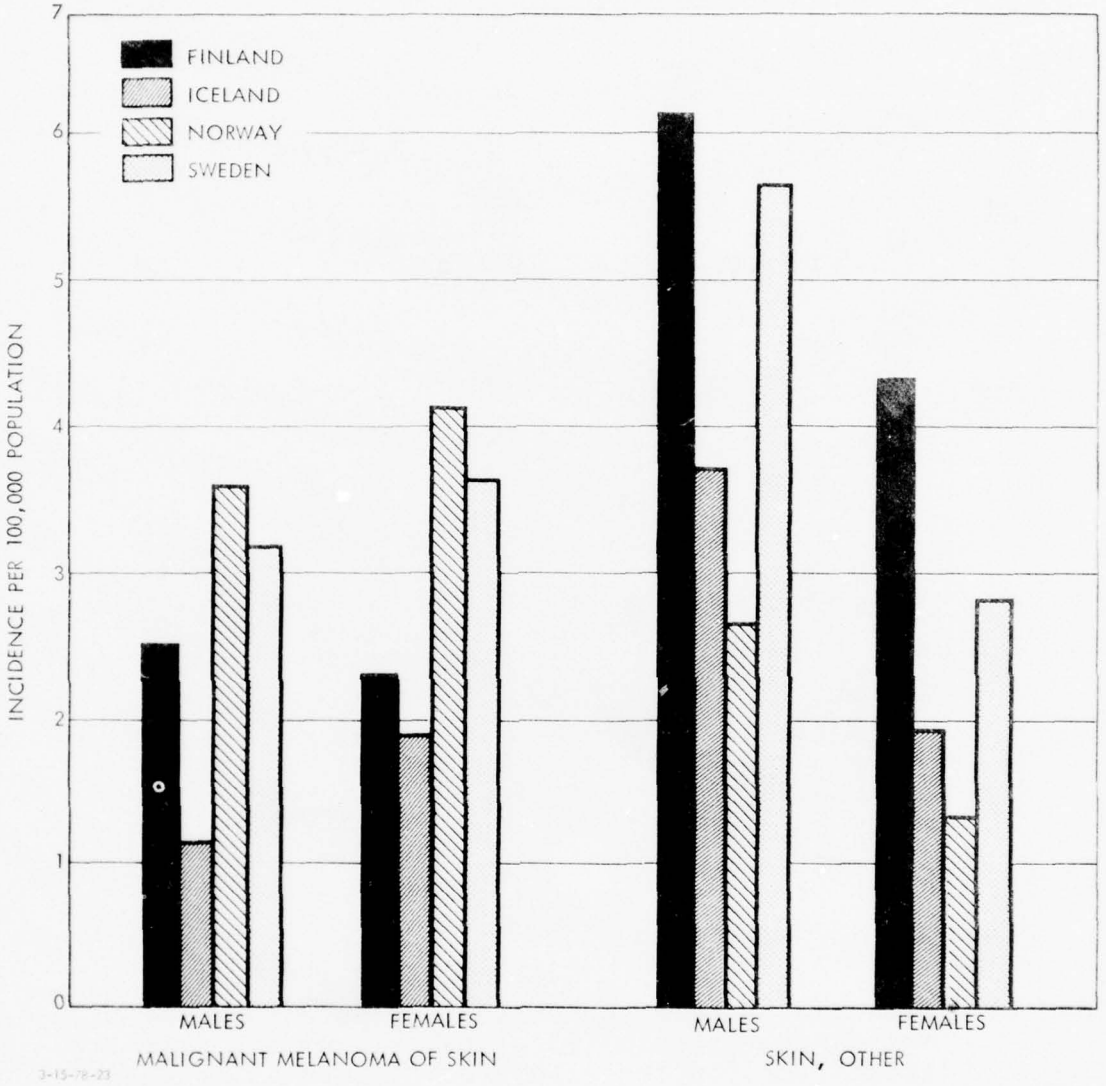
A comparison of the incidence of malignant melanoma and other skin cancer, excluding basal cell carcinomas, by the cancer registries of Finland, Iceland, Norway, and Sweden is shown for the five-year period 1962 to 1966 (1957 to 1966 for Iceland) in Fig. 19 (Ringertz 1971). Note that for females in Norway and Sweden, and males in Norway, the incidence for malignant melanoma was higher than it was for other skin cancer, excluding basal cell carcinoma. The Icelandic male-female ratio was 2:1 for other skin cancer, excluding basal cell carcinoma, but anomalously reversed to 0.6:1 for malignant melanoma.

The highest reported incidence of malignant melanoma in the world was in Queensland, Australia. In 1965 an incidence of 16.5 per 100,000 was reported (Davis et al., 1966). There is evidence of a latitude gradient in Australia in the mortality statistics (H. O. Lancaster, 1956). In Queensland, the death rate in 1964 was 4.3 per 100,000, which was triple the death rate of 1.5 in Victoria (Herron 1969). However, no latitude gradient was found within Queensland itself (Herron 1969).



Source: L. Teppo et al., 1975

FIGURE 18. Melanoma of skin in Finland: mean annual age-adjusted incidence rates in 1961-1969, by sex and province. The stratification indicates relative rates (whole country = 1.00)



Source: Ringertz, 1971

FIGURE 19. Age-adjusted incidence rates of malignant tumors of skin.

3. TIME VARIATIONS

3.1 VARIATIONS OVER A RECENT FIVE-YEAR PERIOD

Skin cancer incidence, in general, has varied as a function of time in a given region as well as geographically for a given period of time. Table 3 presents crude* incidence rates for various Caucasian populations by sex for other skin cancer and malignant melanoma for circa 1965 (R. Doll et al., 1970) and for circa 1970 (J. Waterhouse et al., 1976) as extracted from Vols. II and III, respectively of "Cancer Incidence in Five Continents." Also shown in the last four columns are the ratios of the Vol. III to Vol. II incidence rates. Note that nearly all of the ratios exceed unity for both other skin cancer and malignant melanoma and for both sexes, indicating that both types of cancer have recently been increasing on a worldwide basis. According to this data, for most regions the recent rate of increase of incidence with time has been greater for malignant melanoma than for other skin cancer. The largest increases in malignant melanoma incidence with time were experienced in the Scandinavian countries, Poland, the U.S., Israel (native-born Israelis), and the Canadian provinces of Newfoundland and Quebec, but little if any changes were experienced in Hungary and the Canadian provinces of Alberta and Saskatchewan.

If solar ultraviolet radiation is a significant factor for malignant melanoma as well as other skin cancer, an increase in skin cancer incidence with time in a given region would be indicative of an increase in population exposure with time, and

*not age-adjusted

TABLE 3. CRUDE INCIDENCE VARIATIONS WITH TIME

REGION	VOL. II* OTHER SKIN CANCER M	VOL. II* OTHER SKIN CANCER F	VOL. II* MALIGNANT MELANOMA M	VOL. II* MALIGNANT MELANOMA F	VOL. III* OTHER SKIN CANCER M	VOL. III* OTHER SKIN CANCER F	VOL. III* MALIGNANT MELANOMA M	VOL. III* MALIGNANT MELANOMA F	VOL. III / VOL. II OTHER SKIN CANCER M	VOL. III / VOL. II OTHER SKIN CANCER F	VOL. III / VOL. II MALIGNANT MELANOMA M	VOL. III / VOL. II MALIGNANT MELANOMA F
Canada:												
Alberta	49.6	36.4	2.2	2.5	55.8	42.0	2.2	2.6	1.13	1.15	1.00	1.04
Manitoba	44.8	31.5	2.2	2.8	64.7	51.2	2.6	3.6	1.44	1.63	1.18	1.29
Newfoundland	42.6	23.3	0.9	1.2	40.4	27.2	1.3	1.7	0.95	1.17	1.44	1.42
Quebec	21.0	15.1	1.0	1.3	27.2	20.7	1.3	1.8	1.30	1.37	1.30	1.38
Saskatchewan	97.3	66.4	3.1	4.1	122.6	81.3	3.1	3.8	1.26	1.22	1.00	0.93
U.S.:												
Alameda County	--	--	4.1	4.3	--	--	5.7	7.0	--	--	1.39	1.63
Connecticut	--	--	3.8	3.6	--	--	4.9	4.9	--	--	1.29	1.36
El Paso	112.7	85.9	2.5	2.9	119.9	75.5	3.4	4.8	1.06	0.88	1.36	1.66
Israel	--	--	0.6	1.2	--	--	1.6	2.0	--	--	2.67	1.67
Denmark	27.6	18.1	2.8	3.9	34.4	24.5	3.5	6.0	1.25	1.35	1.25	1.54
Finland	19.9	23.8	2.4	2.4	24.4	30.5	2.9	3.4	1.23	1.28	1.21	1.42
German Democratic Republic (DDR)	41.9	37.9	2.2	2.9	45.7	39.9	2.5	3.3	1.09	1.05	1.14	1.14
Hungary:												
Vas	40.6	40.6	2.2	2.9	39.1	34.4	2.5	2.8	0.96	0.85	1.14	0.97
Szablocs-Szatmar	26.3	28.1	1.6	2.2	23.5	28.7	1.7	1.7	0.89	1.02	1.06	0.77
Norway	--	--	4.3	5.0	--	--	6.3	6.8	--	--	1.47	1.36
urban	--	--	5.4	6.3	--	--	8.1	7.9	--	--	1.50	1.25
rural	--	--	3.6	4.0	--	--	5.1	6.0	--	--	1.42	1.50
Poland:												
Cracow	10.9	13.1	0.8	1.6	13.6	14.8	1.7	2.3	1.25	1.13	2.13	1.44
Katowice	10.8	12.1	1.0	1.0	11.9	12.8	1.2	1.7	1.10	1.06	1.20	1.70
Warsaw City	11.3	13.1	1.5	1.6	10.8	14.1	2.5	2.8	0.96	1.08	1.67	1.75
Warsaw rural	--	--	--	--	6.4	7.9	0.8	0.8	--	--	--	--
Sweden	8.7	4.7	3.9	4.4	10.6	6.5	5.4	6.5	1.22	1.38	1.38	1.48
U.K.:												
Birmingham	34.1	27.2	1.3	2.3	37.3	30.6	1.5	2.7	1.09	1.13	1.15	1.17
Oxford	34.0	23.7	1.4	3.3	37.0	28.2	2.5	3.6	1.09	1.19	1.79	1.09
Sheffield	28.4	23.9	1.2	1.9	32.0	26.6	1.3	2.0	1.13	1.11	1.08	1.05
Southwestern	41.7	29.9	1.9	4.3	45.4	35.3	2.2	5.3	1.09	1.18	1.16	1.23
Liverpool	39.9	28.7	1.1	2.3	39.0	31.0	1.1	2.6	0.98	1.08	1.00	1.13
Yugoslavia:												
Slovenia	16.0	20.5	1.5	2.4	16.9	22.0	1.8	3.3	1.06	1.07	1.20	1.38
Hawaii	0.9	0.4	3.5	3.6	1.2	1.5	4.6	4.8	1.33	3.75	1.31	1.33
New Zealand	--	--	6.2	9.6	--	--	7.5	12.3	--	--	1.21	1.28

*Sources: Waterhouse, J., Muir, C., Correa, P. and Powell, Jean, eds., "Cancer Incidence in Five Continents," Volume III, Lyon, (IARC Scientific Publications No. 15) 1976, and Doll, R., Muir, C., and Waterhouse, J. eds., "Cancer Incidence in Five Continents," Volume II, 1970.

one would expect to also see an increase in the incidence of malignant melanoma. The data of Table 3, by and large, appear to be consistent with this hypothesis. However, as in the case of geographic variations, there are also significant anomalies in the time variations. Among Newfoundland males there was a 5 percent decrease in the incidence of other skin cancer but a 44 percent increase in the incidence of malignant melanoma. Among Saskatchewan females, there was a 26 percent increase in the incidence of other skin cancer but a 7 percent decrease in the incidence of malignant melanoma. The greatest time anomaly appears to be in the El Paso female population where there was a 12 percent decrease in the incidence of other skin cancer and a reported 66 percent increase in the incidence of malignant melanoma. The data from five regions of the United Kingdom have a remarkable consistency, with the exception of the Oxford region male population which had an increase of 79 percent in the incidence of malignant melanoma but only a 9 percent increase in the incidence of other skin cancer.

It is instructive to examine the proposition that the anomalies cited above could be explained as extreme fluctuations in a random process. The Vol. II El Paso incidence rate of 2.9 for malignant melanoma is an average value for the period 1960 to 1966. Since the El Paso white female population is approximately 100,000, the number of cases during this 7-year period is therefore $2.9 \times 7 = 20$. If one assumes a Poisson distribution for this random process, the estimate for two standard deviations would be $2\sqrt{20} = 9$. The 2σ confidence limits on the incidence rate would therefore be 11 to 29 and the upper 2σ confidence limit would correspond to a 45 percent increase, which is 21 percent less than the observed incidence increase of 66 percent reported in Vol. III. Thus, while some of the observed increase could be attributed to noise fluctuations in a random process, it is unlikely that there was not some change in the causal mechanism for malignant melanoma in El Paso between

the periods covered by Vol. II and Vol. III and probably in prior years. That it is also extremely unlikely that the causal mechanism that changed was exposure to solar ultraviolet radiation can be seen by examining the statistics for other skin cancer. The Vol. II value of 85.9 for El Paso women corresponds to 85.9 x 7 = 601 cases during a 7-year period. The 2σ value of $2\sqrt{601} = 49$ yields confidence limits of 552 and 650. The lower 2σ confidence limit corresponds to a decrease of 8 percent, which was exceeded by the 12 percent decrease observed. Since the very strong association of other skin cancer incidence and solar radiation exposure is widely accepted, it can be deduced that El Paso females exposed themselves on the average to solar radiation less after the period of Vol. II than before. One possible reason for this behavior can be found in the increased use of home air conditioning equipment, which did not become common in the U.S. until the post 1960 period. Residents of El Paso may now find relief from the extremely high summer temperatures in their air-conditioned homes. However, another recent change in the life style of the southern U.S. population has been the increase in the construction of home outdoor swimming pools which would have tended to increase outdoor exposure.

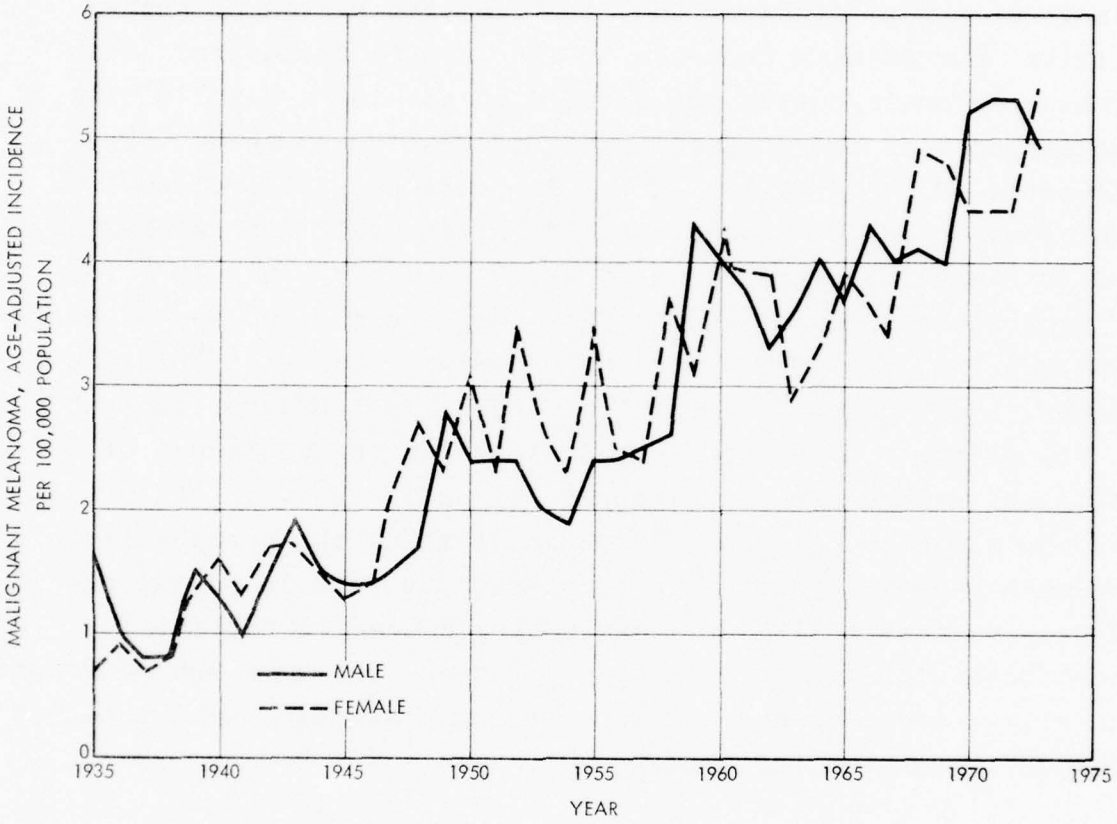
The Oxford region time anomaly for males is very hard to explain, unless there is a large error in the reported value itself. There are 1 million male residents in the Oxford region so that it is highly unlikely that the 79 percent increase in the incidence rate for malignant melanoma can be attributed to a random fluctuation. The next highest incidence increase for males in England was in the southwestern region where the climate is milder and where only a 16 percent increase was registered. It can therefore be reasonably inferred that males in Oxford were being exposed to some extraneous unkown causative factor other than increased solar radiation.

The case for a recent worldwide increase in the incidence of malignant melanoma* is overwhelming from the data of Table 3. This can be seen by making a simple calculation of the probability that the values for all 29 sites for males were the result of random fluctuations, i.e., a site had equal probability of showing a decrease or increase in incidence. This problem is analogous to the problem of tossing a coin 29 times and asking what the probability is of getting 29 heads. The answer is $(0.5)^{29} = 1.8 \times 10^{-9}$. For females, the problem is analogous to asking the probability of one tail (Saskatchewan) and 28 heads. The answer is $29 \times 1.8 \times 10^{-9} = 5.2 \times 10^{-8}$ for a joint probability of 10^{-16}. However, there is no way of asessing from the data of Table 3 the underlying cause of this increase in malignant melanoma incidence. The observation that in the majority of regions the increase in the incidence of malignant melanoma was accompanied by an increase in other skin cancer incidence only serves to not disallow the possibility of a common causative factor in those regions, and in no way excludes the possibility of a coexisting causative factor(s) other than ultraviolet radiation. Indeed, the time and geographic anomalies cited for some regions strongly suggest the existence of such an unknown factor(s).

3.2 LONG-TERM VARIATIONS

By examining long-term variations in incidence in a given region, it is possible to smooth over short-term random fluctuations and obtain a clearer indication of time trends. An excellent illustration of this advantage is shown in Fig. 20 which

*Increases in incidence and mortality from malignant melanoma have been previously observed (J. A. H. Lee, 1976, K. Magnus, 1977, O. M. Jensen, and A. M. Bolander).

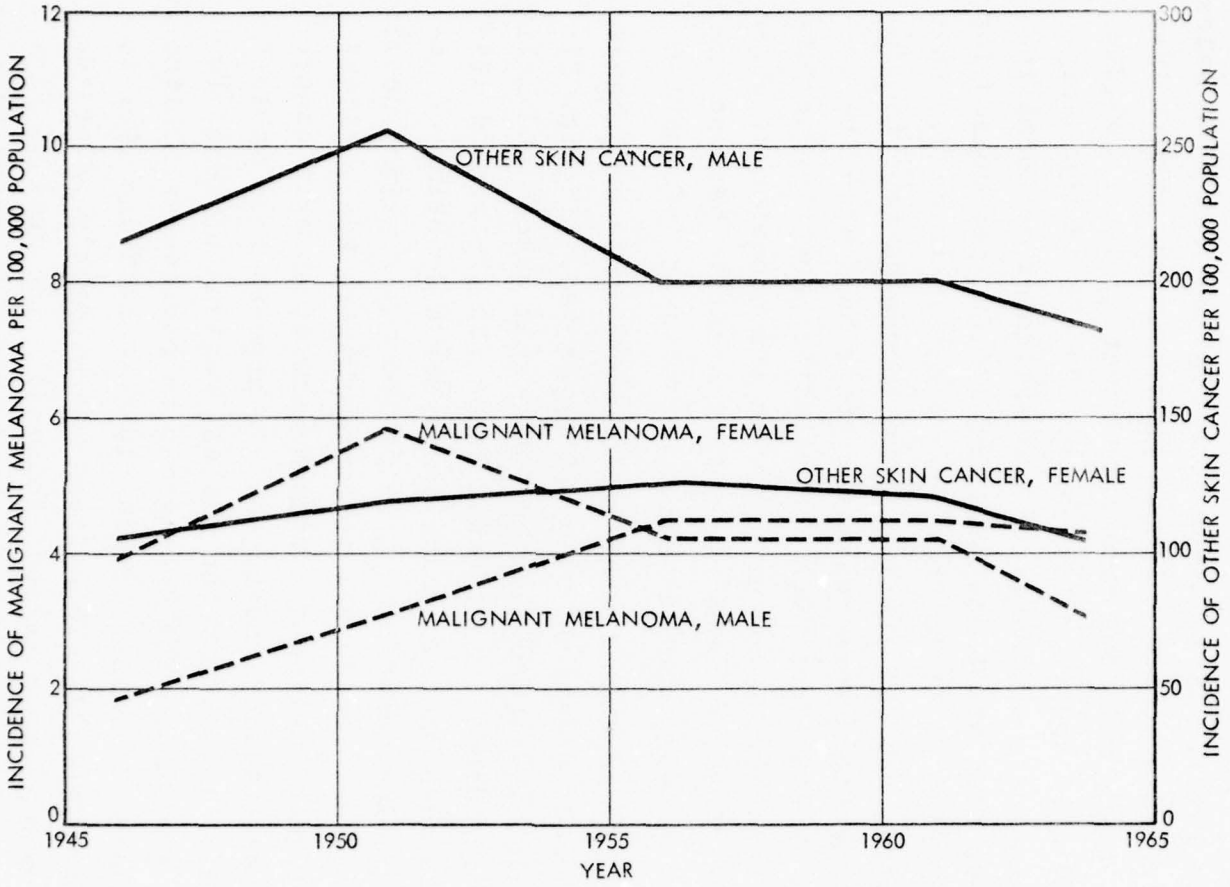


Source: Connecticut Tumor Registry.

FIGURE 20. Age-adjusted incidence of malignant melanoma in Connecticut by sex, 1935-1972

is a plot of the annual age-adjusted incidence in malignant melanoma for the period 1935 to 1973 as tabulated by the Connecticut State Department of Health (H. Eisenberg, 1966, B. Christine et al., 1966 to 1972). It is clear from Fig. 20 that both males and females have experienced a linear growth in the annual incidence of malignant melanoma from approximately 1 per 100,000 in the mid 1930's to approximately 5 per 100,000 in the early 1970's. The time rate of change of the malignant melanoma incidence rate has been about one case per 100,000 per decade for each sex. From Fig. 20 it is therefore possible to deduce that only approximately half of the incidence increases reported in Table 3 for Connecticut were real; the other half were the result of random fluctuations over the relative short 5-year time period. Unfortunately, a comparison with the behavior of other skin cancer incidence in Connecticut is impossible because the Connecticut State Department does not record such information.

There are few regions in the world where other skin cancer incidence has been registered over a long period. In Fig. 21 (E. J. MacDonald, 1976) are plotted other skin cancer and malignant melanoma incidence for El Paso, Texas for the period 1944 to 1966. It is seen that in males there was a doubling of malignant melanoma incidence over this period but a slight decline in other skin cancer incidence; in females there was a slight decline in malignant melanoma incidence and other skin cancer incidence was essentially unchanged. It appears from Table 4 (E. J. MacDonald, 1976) that for the six regions of Texas for which data is available, the only group to register a decline in malignant melanoma incidence between 1944 to 1948 and 1962 to 1966 was El Paso females. This trend was evidently reversed over the following 5-year period (Table 3). The data of Fig. 21 and Table 4 are age-standardized to the 1970 U.S. population and cannot be directly compared to the data of Table 3 which was age-standardized to a European population. While the relatively small populations of these regions lead to large fluctuations



Source: E. J. MacDonald, 1976.

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FIGURE 21. Malignant melanoma and other skin cancer, age-adjusted incidence rates in El Paso

compared to the data from the state of Connecticut, the weight of the data suggests that there has been a substantial increase in the incidence of both other skin cancer and malignant melanoma over this 2-decade period in Southern Texas.

TABLE 4. AGE-ADJUSTED INCIDENCE RATES FOR SIX REGIONS IN TEXAS

REGION	1944-48				1962-66				1962-1966 / 1944-48			
	OTHER SKIN CANCER		MALIGNANT MELONOMA		OTHER SKIN CANCER		MALIGNANT MELANOMA		OTHER SKIN CANCER		MALIGNANT MELANOMA	
	M	F	M	F	M	F	M	F	M	F	M	F
El Paso	216	107	1.9	4.0	183	106	4.3	2.9	0.84	0.99	2.26	0.73
San Antonio	55	36	2.9	3.1	147	90	8.2	7.9	2.67	2.50	2.83	2.54
Laredo	34	23	6.9	0.9	2.57	131	10.3	5.7	7.56	5.70	1.49	6.33
Harlingen	16	8	2.8	2.4	285	139	6.8	7.4	17.8	35.6	2.43	3.08
Corpus Christi	106	47	2.6	4.7	371	207	7.0	6.8	3.50	4.40	2.69	1.45
Houston	40	19	2.6	2.2	93	44	7.3	9.0	2.33	2.32	2.81	4.09

In Finland, over the period 1953 to 1973, the incidence of malignant melanoma (Fig. 22) has approximately doubled for both males and females (L. Teppo et al.). This trend is in excellent agreement with that of Connecticut (Fig. 20) which has a population of approximately the same size. This example again demonstrates the advantage of examining long-term trends, for the 5-year time trend for Finland (Table 3) indicated that melanoma for females was increasing at twice the rate for males. Comparing this long time trend with that for other skin cancer, excluding basal cell carcinoma, an entirely different behavior is found. From 1953 to 1960 there was a sharp rise in other skin cancer, excluding basal cell carcinomas, followed by a sharp and prolonged drop for both sexes. The latter divergent trend represents a striking anomaly in the linkage of solar radiation exposure to malignant melanoma.

In Norway, over the period 1955 to 1973, the incidence of malignant melanoma (Fig. 23) has approximately tripled (K. Magnus, 1975) for both sexes. Other skin cancer data is not available from Norway over this time period. The higher rate of increase for malignant melanoma incidence in Norway compared to Finland or Connecticut may be related to a higher genetic susceptibility among Norwegians. The observation that Norwegians are known to be genetically more susceptible to other skin cancer and may also be more susceptible to malignant melanoma is consistent with the hypothesis linking solar radiation to malignant melanoma, but, again, this does not rule out the possible existence of some other unknown causative factor.

In Denmark, over the period 1943 to 1972 (J. Clemmesen, 1977) there has been a sharp increase in the incidence of malignant melanoma (Fig. 24), but the incidence in females has been rising at a faster rate than in males, particularly after 1955. While the incidence of other skin cancer has also been increasing for both sexes in Denmark during this period (Table 3), there remains the anomaly of an inversion in the incidence sex ratio for the two types of tumors.

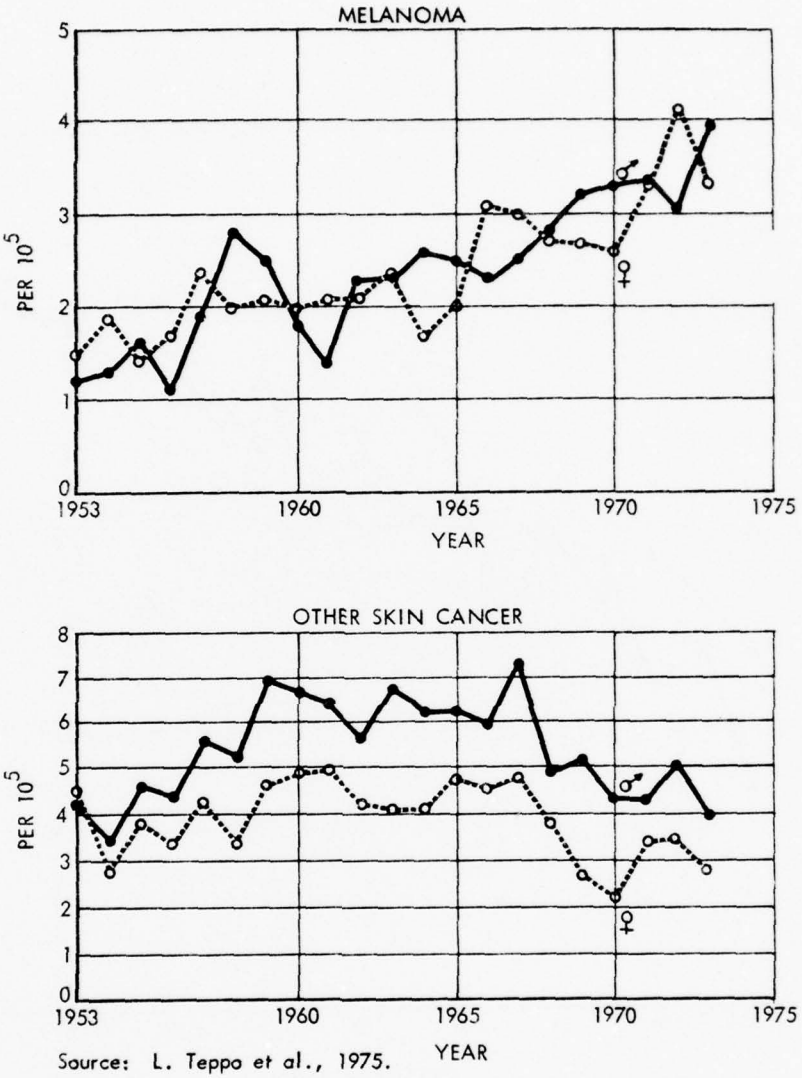
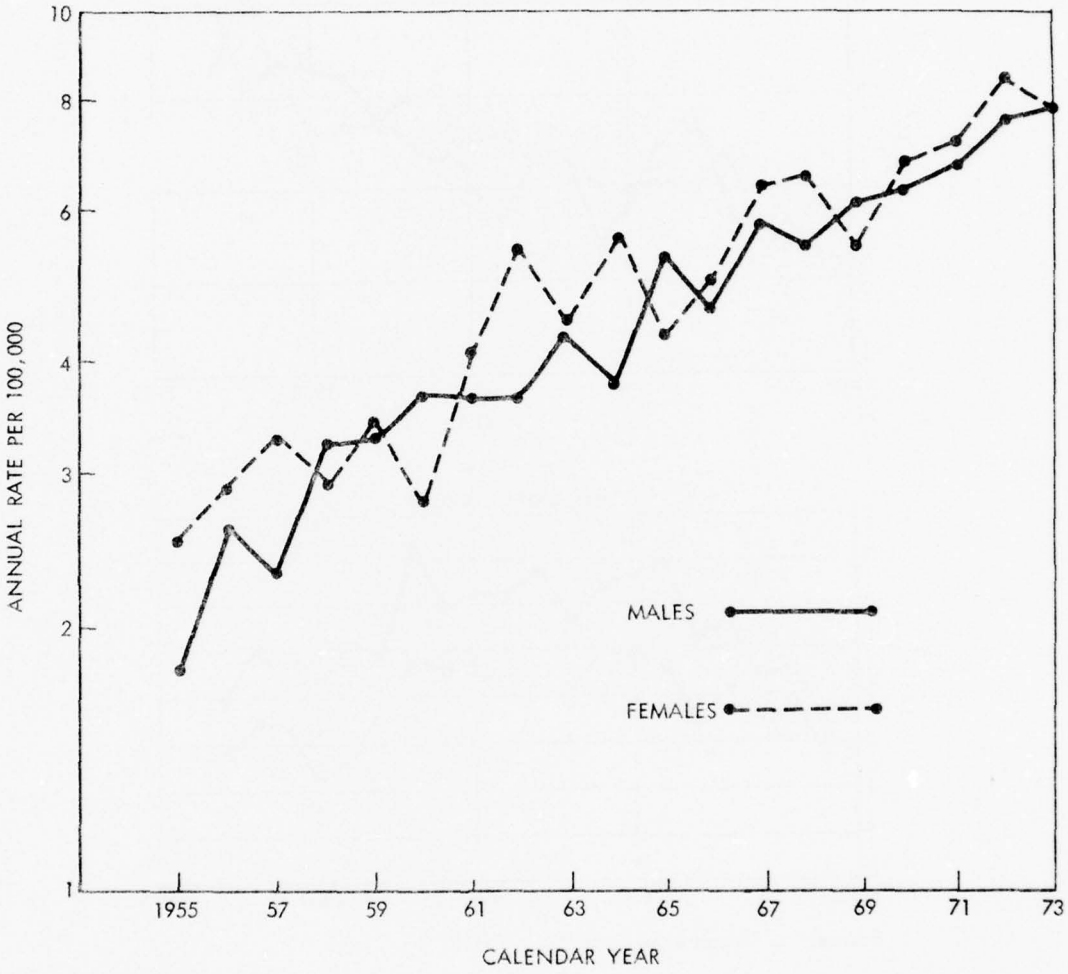


FIGURE 22. Annual age-adjusted incidence rates (per 10^5) of cutaneous melanoma and other cancers of the skin (excluding basal cell carcinomas) in Finland in 1953-1973, by sex



Source: K. Magnus, 1975.

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FIGURE 23. Total age-adjusted incidence rate of maligant melanoma of the skin in Norway 1955-1973 by calendar year

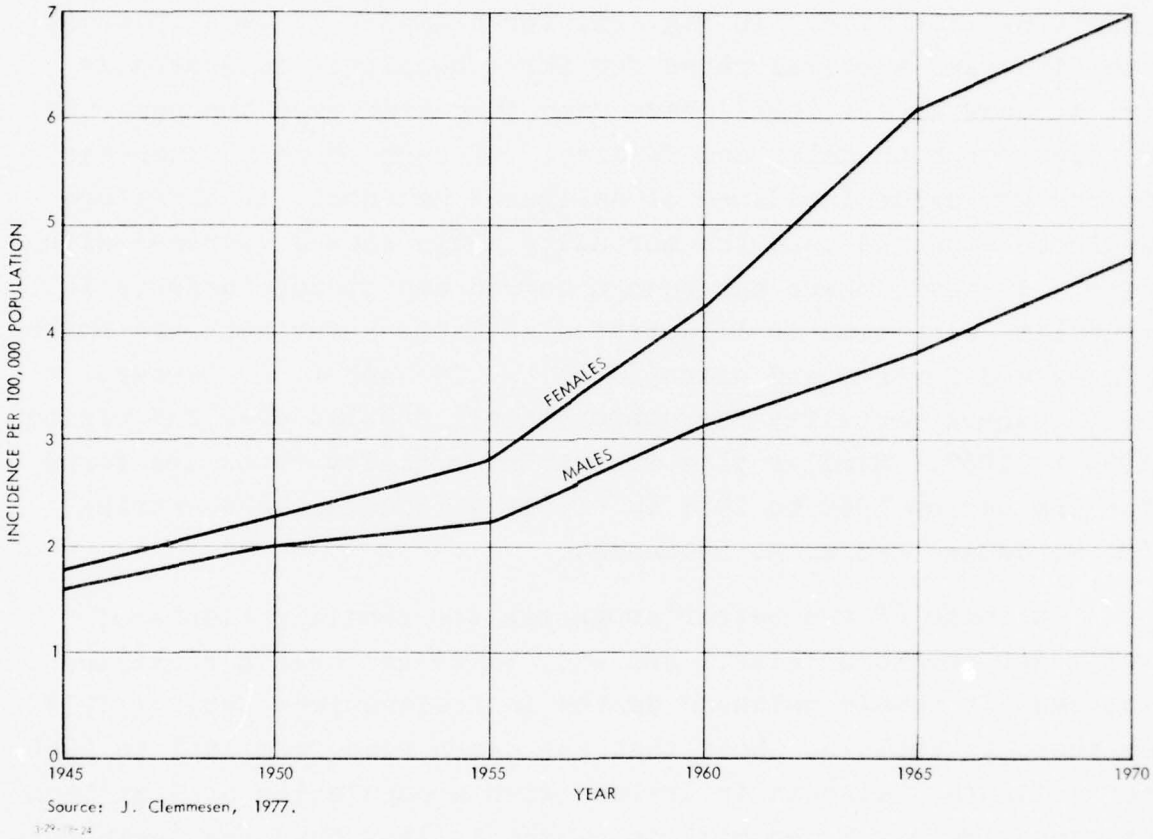
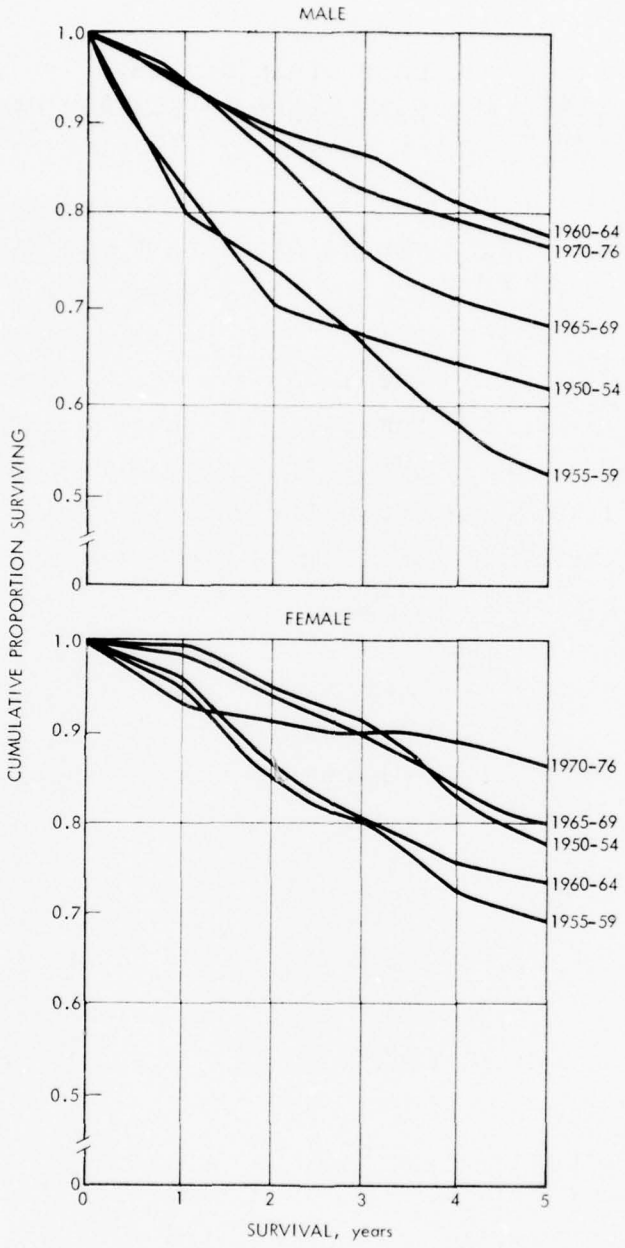


FIGURE 24. Incidence of malignant melanoma in Denmark

3.3 MORTALITY VARIATIONS

Additional strong evidence of an increase in the worldwide incidence of malignant melanoma can be obtained from an examination of the time trends in mortality statistics which should be more accurate than the incidence statistics. There is evidence that shows that the effectiveness of melanoma treatment has been improving with time. In Fig. 25, for example, it is seen that the five-year survival rates for three hospitals in Australia (H. M. Shaw et al., 1977) have been improving over the past two decades for both males and females. If there were no increase in the worldwide incidence of malignant melanoma, it therefore would be expected that the mortality would show a decrease with time. Instead, there has been a marked and steady increase in mortality with time as illustrated in Table 5 for both the United States and England and Wales (J. A. H. Lee and A. P. Carter, 1970), where mortality has approximately doubled over the period 1950 to 1967. Similar time trends in mortality rates are found for the period 1960 to 1973 in nearly all Caucasian countries (O. M. Jensen and A. M. Bolander).

In spite of the better prognosis for female patients of malignant melanoma (Figs. 6 and 25), there has been a startling increase in female melanoma deaths in Ireland from 1961 to 1974 as shown in Table 6. Note that the death rate from 1961 to 1964 for malignant melanoma in Ireland with a population of 3 million is approximately 7 per million, which is less than the death rate of approximately 11 in nearby England and Wales during that time period. This comparison between countries with large populations casts serious doubt on the validity of the Australian survey indicating that people of Celtic background are genetically almost twice as susceptible to malignant melanoma (M. M. L. Brown et al., 1971) as those of predominantly British extraction.



Source: H. M. Shaw et al., 1977.

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FIGURE 25. Cumulative survival rates of all male and female patients seen divided by calendar period in Australia

TABLE 5. SECULAR TRENDS OF DEATH RATES FROM MALIGNANT MELANOMA: U.S. WHITES AND ENGLAND AND WALES*

YEAR	U. S.	ENGLAND and WALES
1950	9.3	5.1
1951	10.0	5.7
1952	10.2	6.7
1953	11.3	6.8
1954	11.8	7.4
1955	12.0	8.5
1956	11.7	7.3
1957	12.4	8.7
1958	12.5	7.8
1959	12.8	8.4
1960	13.4	8.5
1961	13.9	8.4
1962	13.5	9.0
1963	14.0	9.0
1964	15.3	9.9
1965	15.3	10.4
1966	15.4	10.2
1967	16.0	10.2

*All rates per million per year.

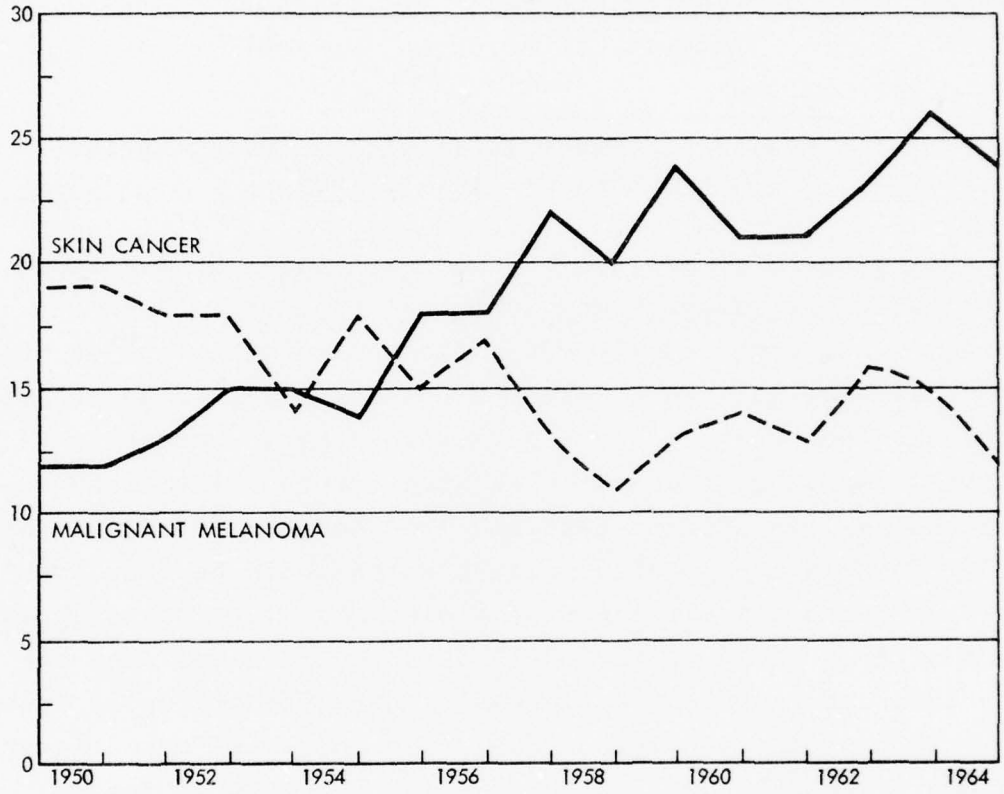
TABLE 6.* NUMBER OF DEATHS FROM MALIGNANT MELANOMA IN IRELAND

	MALE	FEMALE
1961	14	9
1964	12	9
1974	17	21

*Personal Communication with J. Dean, Social Medical Board, Dublin, Ireland

A time trend comparison of the death rates in Australia due to malignant melanoma and other skin cancer is shown in Fig. 26 (W. H. Ward, 1967). Over the period 1950 to 1964 the death rate from malignant melanoma has doubled whereas the death rate from other skin cancer has decreased by 50 percent. Almost identical behavior in death rates were reported for Canada between the periods 1951 to 1955 and 1966 to 1970 (J. A. H. Lee, 1976). This is an anomalous result which would be consistent with the hypothesis linking ultraviolet radiation to malignant melanoma if it could be shown (1) that the survival rate for other skin cancer has been increasing at a significantly faster rate than the appreciable survival rate increase for malignant melanoma (Fig. 25), or (2) the fraction of cases of deaths erroneously attributed to other skin cancer has been decreasing with time. A study in California found that instead of the 130 deaths coded to skin cancer in 1959, the true number was probably between 40 and 50 (J. E. Dunn, et al., 1965).

In the U.S. over the period 1960 to 1967 the death rate due to malignant melanoma increased by 20 percent, while the death rate due to other skin cancer decreased by 8 percent (J. A. H. Lee and A. P. Carter, 1970). The combined effect in the U.S. is a stable death rate from all primary malignant tumors of the skin over the period 1950 to 1968 of 3 per 100,000 in males and 2 per 100,000 in females (J. A. H. Lee, 1972). In England and



Source: W. H. Ward, 1967.

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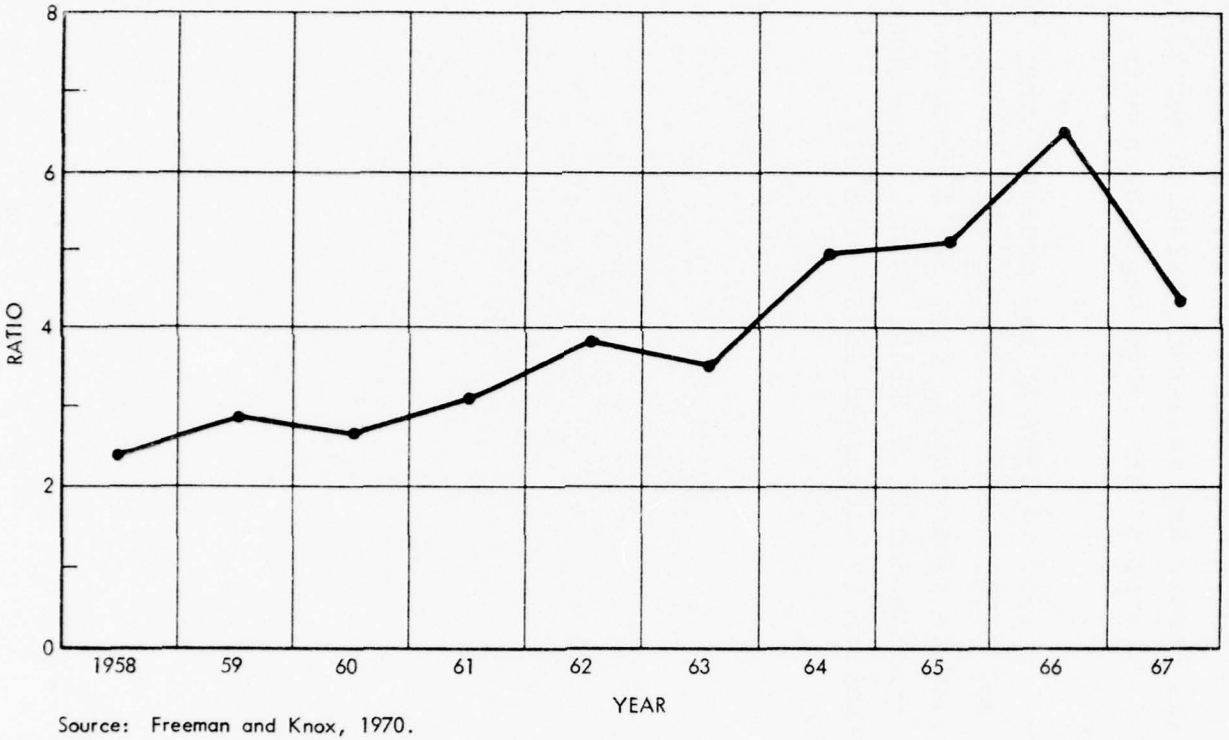
FIGURE 26. Deaths due to malignant melanoma of skin and other skin cancers in Australia. Rate per million of population.

Wales between the periods 1951 to 1955 and 1961 to 1965 the death rate due to malignant melanoma increased by 33 percent, while the death rate due to other skin cancer decreased by 30 percent (J. A. H. Lee and A. P. Carter, 1970). Diverging time trends in other skin cancer and malignant melanoma mortality are therefore found in most of the large English-speaking nations of the world.

During the period 1957 to 1967 it was observed that for 257 squamous cell and 1,045 basal cell carcinomas in Houston, Texas the basal squamous tumor ratio (Fig. 27) increased significantly (R. G. Freeman and J. M. Knox, 1970). The probable reason for this behavior is discussed in Section 6.2.



Source: Freeman and Knox, 1970.

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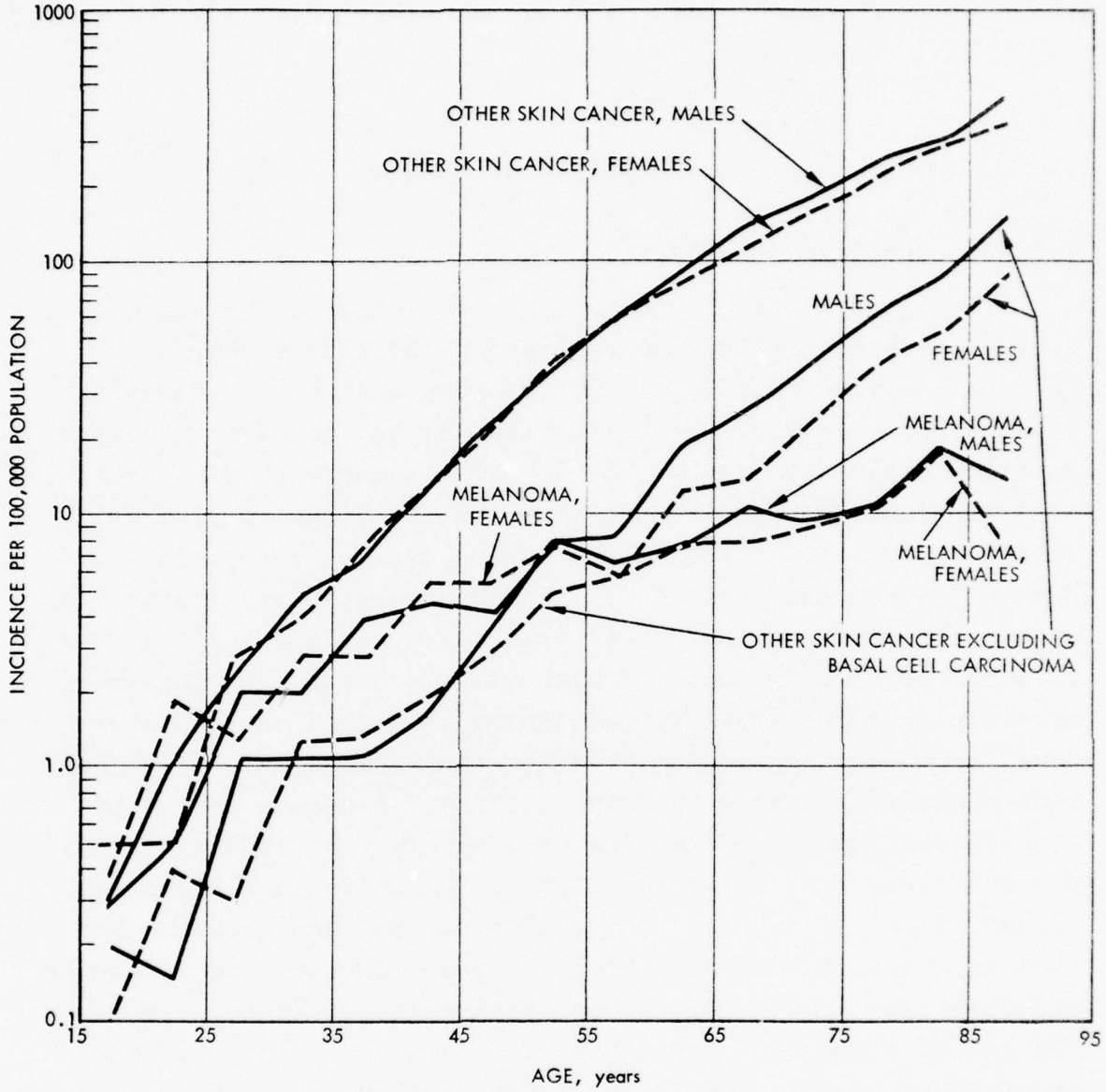
FIGURE 27. Basal/squamous skin tumor ratio in Houston

4. AGE VARIATIONS

4.1 AGE-SPECIFIC INCIDENCE

The age-specific incidence rate for other skin cancer, i.e., incidence per 100,000 population for each 5-year age group, increases rapidly with increasing age for all Caucasian populations. In Fig. 28 are plotted the age-specific incidence rate for other skin cancer, other skin cancer excluding basal cell carcinoma, and malignant melanoma (L. Teppo et al., 1975, Waterhouse et al., 1976) in the period 1966 to 1970. The behavior of the other skin cancer incidence rates was consistent with the hypothesis that other skin cancer incidence is a function of the lifetime dose of ultraviolet radiation. The age-specific incidence rate for malignant melanoma, on the other hand, behaved in an entirely different fashion. It was higher than other skin cancer in young adults, but much lower in the elderly population, increasing very slowly for persons over 40 years of age. The age-specific rate for males in Finland was almost identical to that for females for all age groups. For persons older than approximately 45 years of age, the incidence of other skin cancer, excluding basal cell carcinoma, was significantly higher for males than for females. Since the age-specific rates for other skin cancer, including basal cell carcinoma, were very close for males and females, it could be deduced that the basal cell male/female ratio was approximately equal to unity in Finland. This is in sharp contrast to the basal cell male/female ratios found for four regions in the U.S. (F. Urbach and J. Scotto, 1975) which fell in the narrow range 1.60 to 1.92. This suggests the strong likelihood that basal cell carcinomas were being significantly under-reported in



Sources: L. Teppo et al., 1975 and Waterhouse, J., Muir, C., Correa, P. and Powell, Jean, eds., "Cancer Incidence in Five Continents, Volume III", Lyon, (IARC Scientific Publications No. 15) 1976.

3-29-78-26

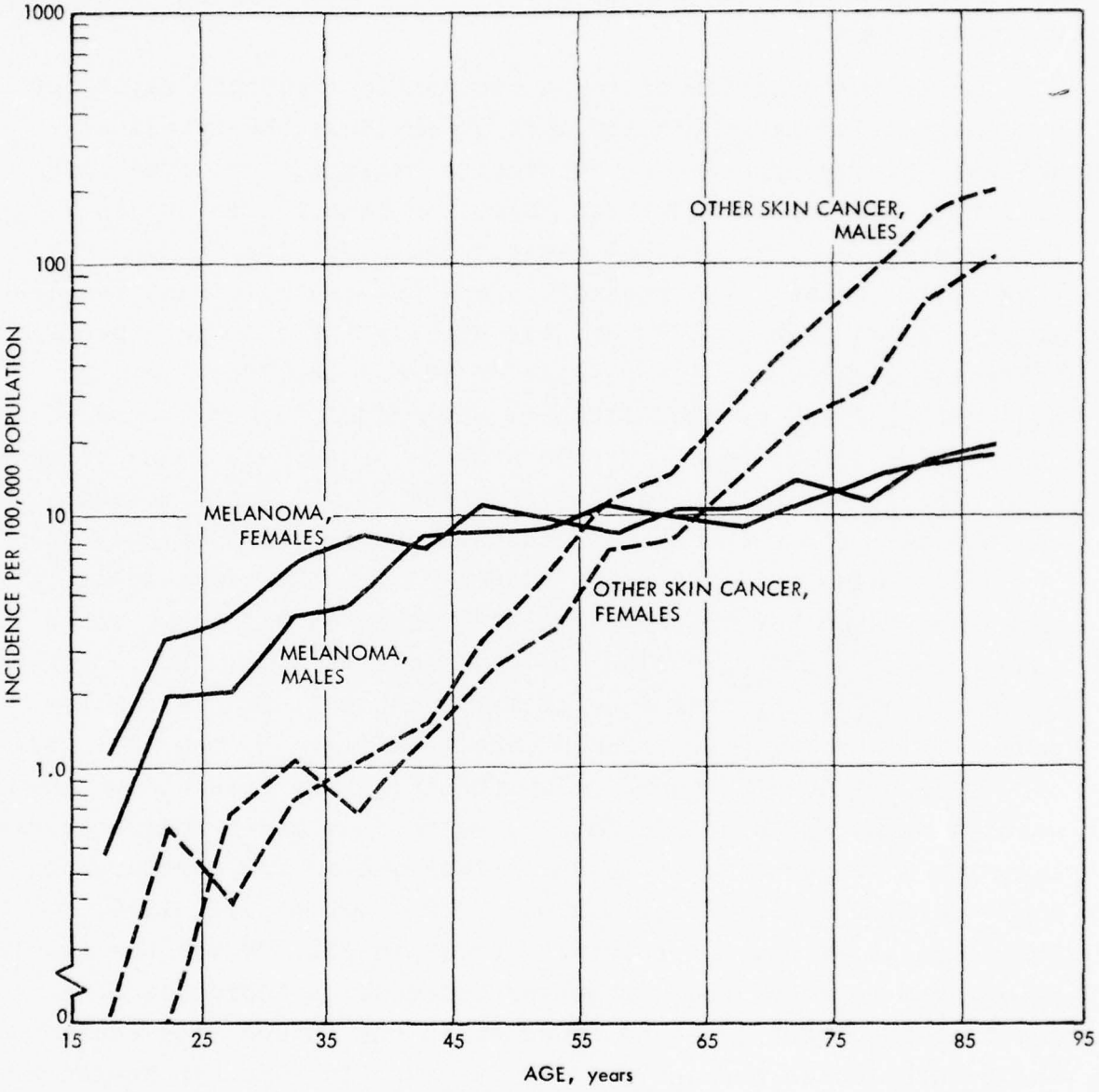
FIGURE 28. Age-specific incidence rates in Finland for malignant melanoma and other skin cancer in 1966-1970

Finland. Below 45 years of age, the risk of malignant melanoma in Finland was appreciably higher than other skin cancer, excluding basal cell carcinoma, but above 45 years of age the risk was much lower.

While the behavior of the age-specific incidence rates for malignant melanoma in Finland clearly indicate the unreasonableness of any hypothesis accociating malignant melanoma with lifetime ultraviolet radiation dose, the behavior in Sweden (J. Waterhouse et al., 1976) clearly calls for its demise (Fig. 29). Between the ages of 45 and 65 both males and females in the period 1966 to 1970 had essentially the same age-specific malignant melanoma incidence rate of 10 per 100,000, i.e., a Swede of 65 years of age, although having had 20 more years of exposure to solar radiation than a Swede of 45,* was found to be at no greater risk. In Sweden, the risk of malignant melanoma was the same for each sex for adults above 40 years of age; below 40, females ran a somewhat higher risk. These age-specific rates are based, of course, on a wide range of different birth cohort data collected during the same span of time. For a given birth cohort group, incidence of malignant melanoma is a monotonically increasing function of age (see Figs. 35 and 36). By modelling the dose-response relationship, it is possible to investigate how age-specific rate curves affect birth cohort curves, assuming a progressive decrease or increase in the carcinogenic esposure over a given time period (P. J. Cook et al., 1969). The flatness of the age-specific curves in Fig. 29 for the middle-aged group suggests that, whatever increase in incidence of a given birth cohort is to be expected in the future, its cause can be attributed primarily to an increase in some carcinogenic agent(s) in the environment, but not to an increase in population exposure to solar ultraviolet radiation.

In Fig. 30 are plotted the age-specific incidence rates for Geneva, Switzerland in 1970 to 1972 (J. Waterhouse et al., 1976).

*as evidenced by the order of magnitude higher other skin cancer incidence rate for a 45 year old Swede compared to a 60 year old.



Source: Waterhouse, J., Muir, C., Correa, P. and Powell, Jean, eds., "Cancer Incidence in Five Continents, Volume III", Lyon, (IARC Scientific Publications No. 15) 1976.

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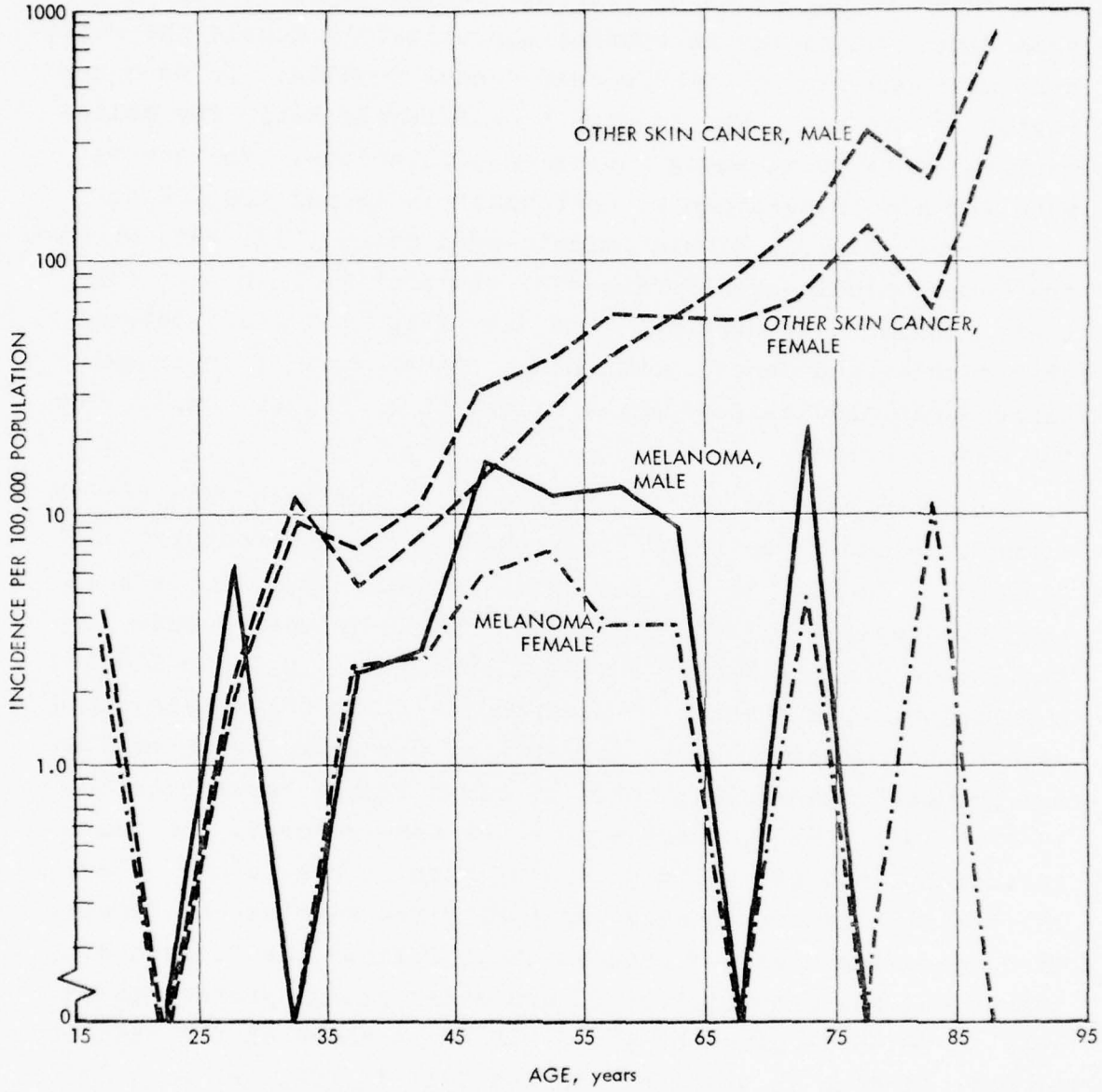
FIGURE 29. Age-specific incidence rates in Sweden for malignant melanoma and other skin cancer (excluding basal cell carcinoma) in 1966-1970



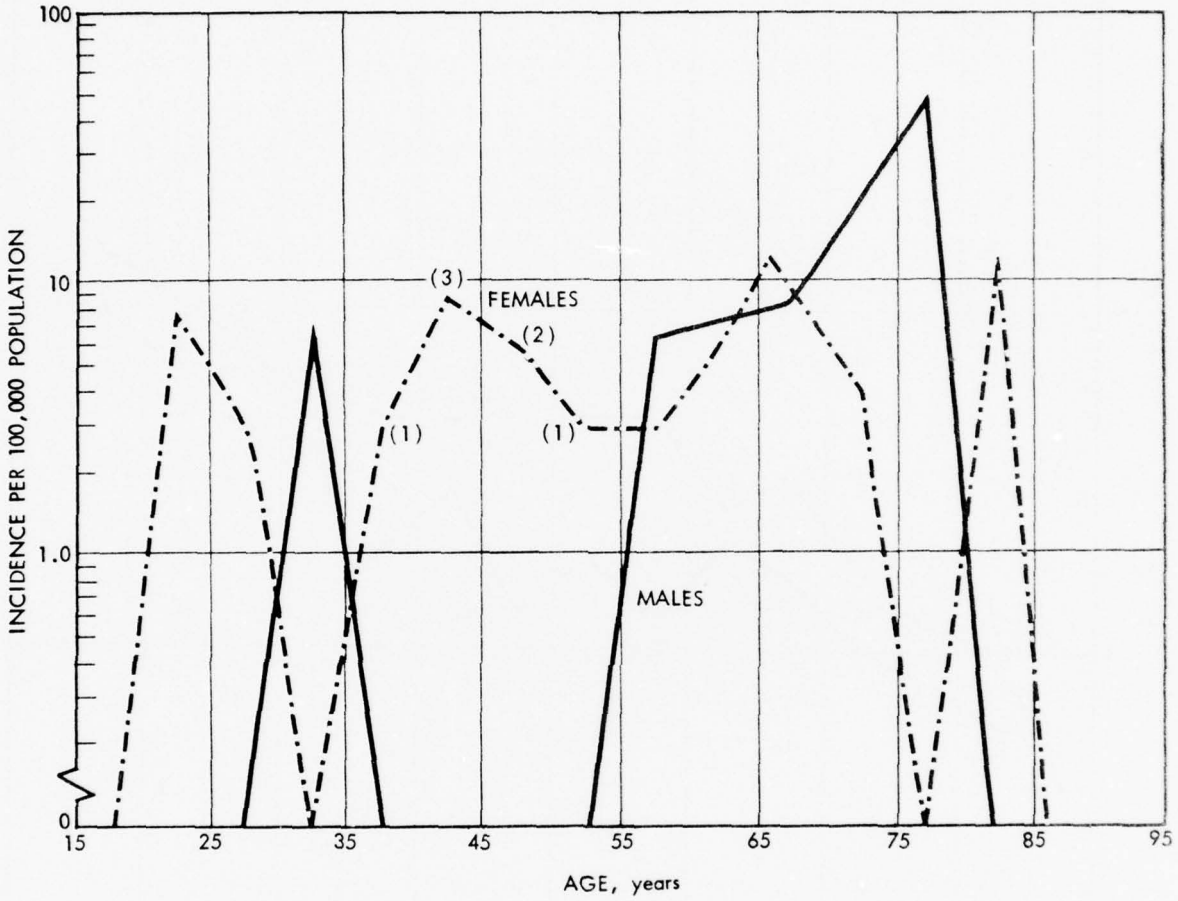
Source: Waterhouse, J., Muir, C., Correa, P. and Powell, Jean, eds., "Cancer Incidence in Five Continents, Volume III", Lyon, (IARC Scientific Publications No. 15) 1976.

3-29-78-28

FIGURE 30. Age-specific incidence rates in Geneva for malignant melanoma and other skin cancer in 1970-1972

The relatively small population of Geneva (330,000) leads to rather noisy curves, but the consistency of the malignant melanoma rates in the 45 to 65 year age region suggests that middle-aged Geneva males may be running approximately double the malignant melanoma risk of middle-aged Geneva females. In no other region of the world was so high a male/female ratio for malignant melanoma found among Caucasian populations. The Geneva rate for middle-aged men of approximately 10 per 100,000 exceeded the rate for Finnish middle-aged males (Fig. 28), whereas the Geneva middle-aged female rate was smaller than that for their Finnish counterparts. The data (Fig. 30) also indicate that middle-aged Geneva women had a higher rate of other skin cancer than middle-aged Geneva males, thus further compounding the Geneva anomaly.

Another anomaly in the age-specific incidence rate for malignant melanoma was found in Ayrshire, Scotland (population 370,000). In Fig. 31 (J. Waterhouse et al., 1976) it is seen that middle-aged (35 to 55) females had an incidence rate very similar to that of Geneva females, approximately 5 per 100,000 population. The numbers in parentheses along the female curve denote the number of cases for each of the four 5-year middle age groups. There was a total of seven female cases over the 1970 to 1972 period, whereas no cases were reported for males. An insight into how valid a finding this is can be had by assuming the male incidence rate was really the same as the female. Then, assuming a random process which follows the Poisson distribution, the probability of zero cases among Ayrshire males aged 35 to 55 is given by e^{-7} or 10^{-3}. A check on the validity of this finding is available in the Vol. II (Doll et al., 1970) data for 1963 to 1966 in Scotland (Fig. 32) which then had a population of 5.3 million. Note that the assumed seven expected cases in the 35 to 55 age group is greater than the 2.2 one would have expected had Ayrshire males followed the incidence rate for all Scottish males (see parenthesis in Fig. 32). The probability of zero cases in Ayrshire is therefore reduced to



Source: Waterhouse, J., Muir, C., Correa, P. and Powell, Jean, eds., "Cancer Incidence in Five Continents, Volume III", Lyon, (IARC Scientific Publications No. 15) 1976.

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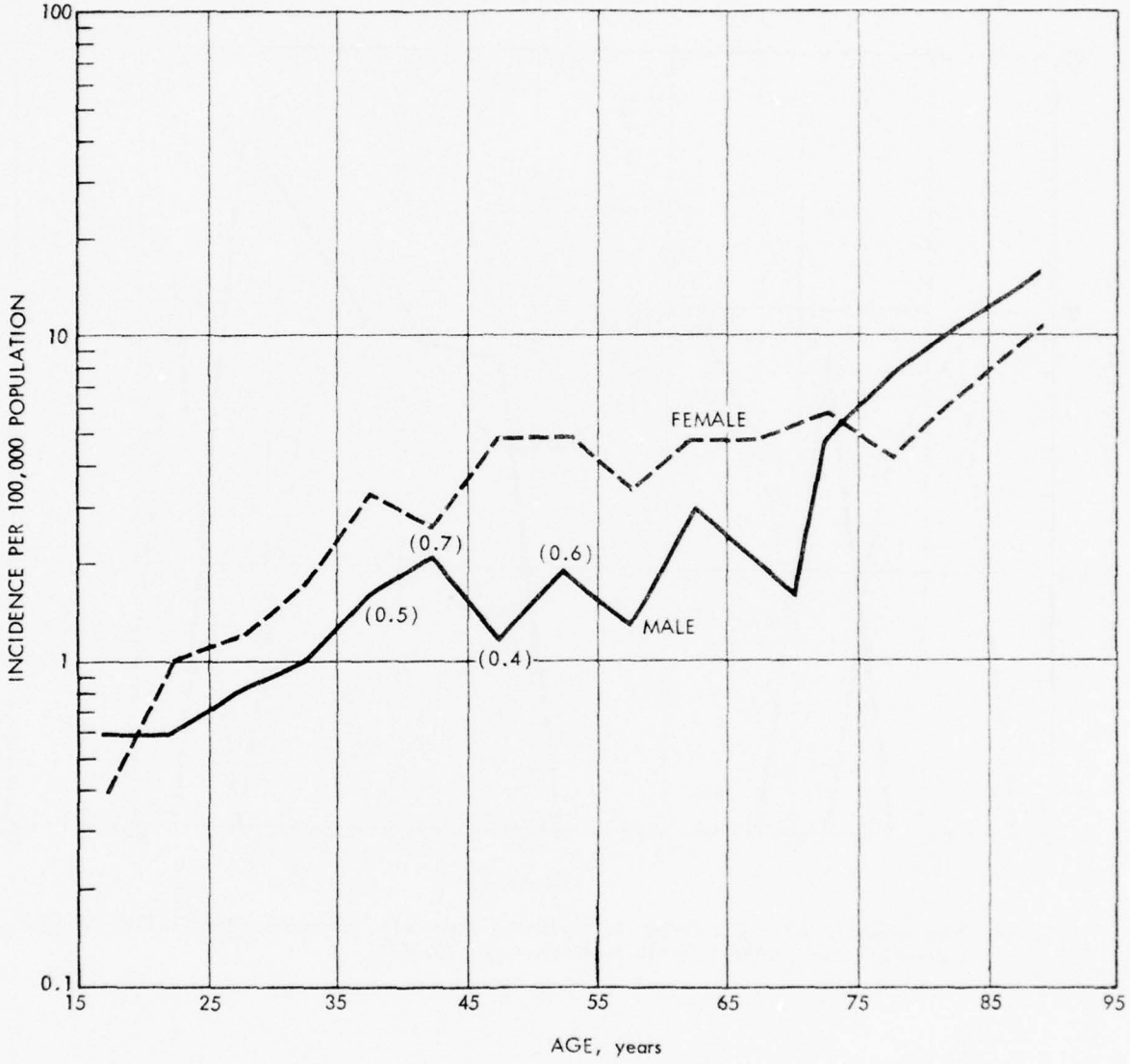
FIGURE 31. Age-specific incidence rates in Ayrshire, Scotland for malignant melanoma in 1970-1972



Source: Howitt, L. F., "Cancer Incidence in Scotland 1963-1966." In: Doll, R., Muir, C., and Waterhouse, J., eds., "Cancer Incidence in Five Continents, Volume II," 1970.

3-30-78-12

FIGURE 32. Age-specific incidence rates in Scotland for malignant melanoma in 1963-1966

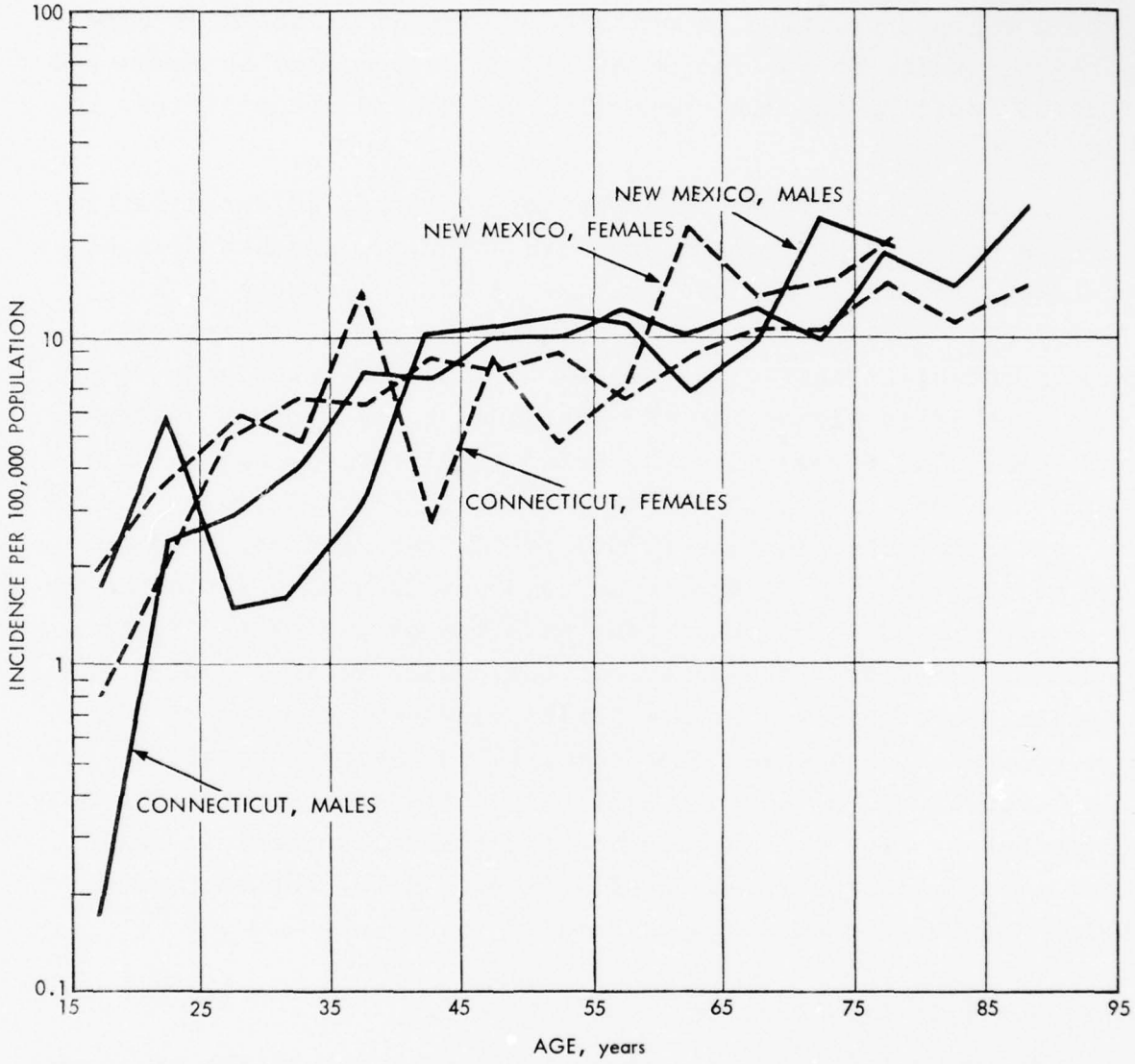
$e^{-2.2}$ or 0.11. However, the more important conclusion to be drawn from Fig. 32 is that male Scots under the age of 70 did indeed enjoy a relative immunity to malignant melanoma as compared to female Scots (factor of 2) and as compared to males and females residing in more northerly Finland and Sweden (Figs. 28 and 29).

A comparison of the age-specific malignant melanoma rates for Connecticut, a northern state in the U.S., and New Mexico, a southwestern state, is made in Fig. 33 (J. Waterhouse et al., 1976). The small New Mexico population of 530,000* (approximately one-sixth that of Connecticut) leads to relatively noisy data, but it is clear that the incidence rates for both males and females were very close to being equal for all age groups. From this comparison, it can be reasonably deduced that not only is malignant melanoma not related to a lifetime dose of solar ultraviolet radiation, but to acute doses as well. For an acute dose hypothesis to be consistent with the data of Fig. 33, it would be necessary to assume that the number of acute solar radiation doses received by New Mexico males and females of all age groups matched the number received by their Connecticut counterparts who lived in an entirely different climatic and solar environment. The probability that such an assumption is valid cannot be calculated because of a lack of data, but one would think it would be exceedingly small.

4.2 Age-Specific Mortality

The death rates from malignant melanoma by age for the sexes combined in England and Wales, 1951 to 1955 and 1961 to 1965, are shown in Fig. 34 (J. A. H. Lee and A. P. Carter, 1970). The death rate during that decade is seen to have increased most among the middle-aged. From these data it can be deduced that

*Excludes Spanish/Latin and American Indian residents.



Source: Waterhouse, J., Muir, C., Correa, P. and Powell, Jean, eds., "Cancer Incidence in Five Continents, Volume III", Lyon, (IARC Scientific Publications No. 15) 1976.

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FIGURE 33. Age-specific rates in Connecticut (1968-1972) and New Mexico (1969-1972) for malignant melanoma

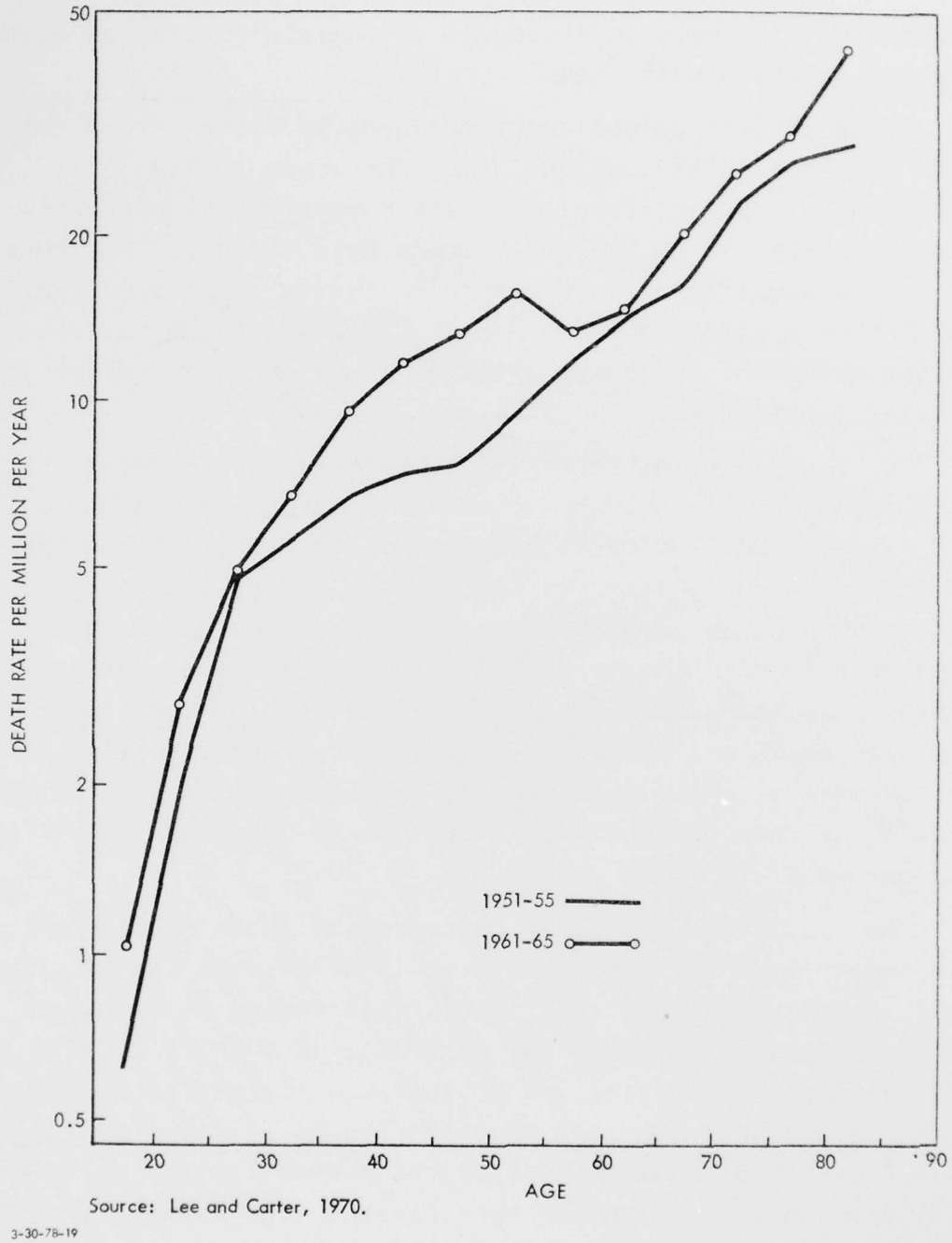


FIGURE 34. Death rates from malignant melanoma by age: sexes combined. England and Wales, 1951-55 and 1961-65.

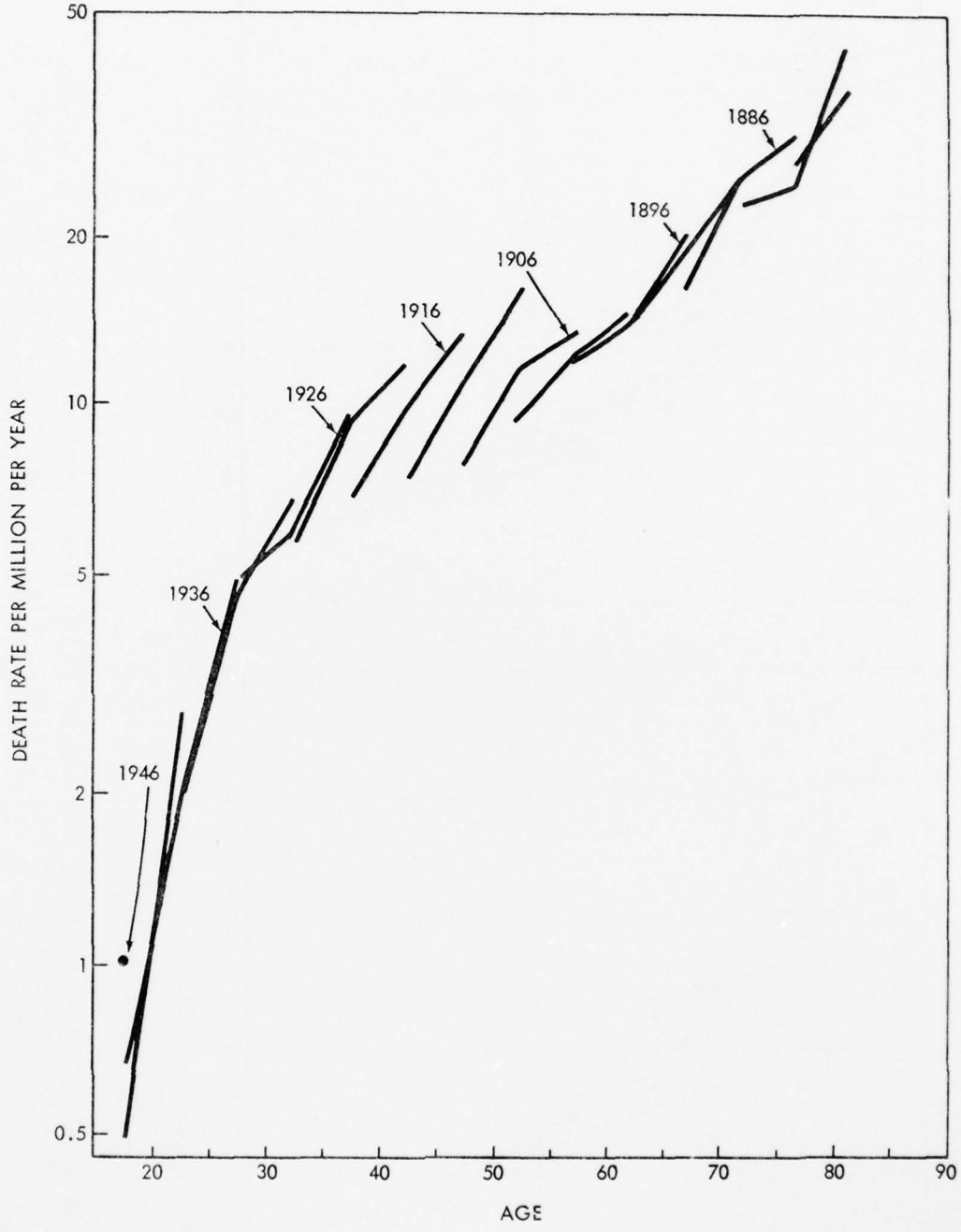
the greatest increase in incidence of malignant melanoma also occurred in the middle-aged.

Death rates from malignant melanoma by birth cohort for the sexes combined in England and Wales are shown in Fig. 35 (J. A. H. Lee and A. P. Carter, 1970), and separately for Finnish males and females in Fig. 36 (L. Teppo). These data indicate that there has been a significant increase in incidence of malignant melanoma for each 5-year birth cohort. Clearly, the pernicious agent causing malignant melanoma, whatever it may be, has become increasingly potent for all adult age groups.

In Fig. 37 (W. H. Ward, 1967) are shown death rates by age group in Australia in 1955 for malignant melanoma and other skin cancer. The Australia melanoma death rate exceeded the other skin cancer death rate for all age groups younger than 70, but the skin cancer death rate greatly exceeded the melanoma death rate in the elderly population. Since the members of the younger population were being lost in greater numbers to melanoma, they were being deprived of a much longer productive life than the elderly lost to other skin cancer. Malignant melanoma therefore poses a far more serious health problem for society than other skin cancer.

The U.S. death rates due to malignant melanoma and other skin cancer over the period 1950 to 1969 are shown in Fig. 38 (T. J. Mason et al.) by sex. It is interesting to compare these mortality rates with those for Australia in 1955 (Fig. 37). The similarities are striking: a 60-year-old Australian in 1955 ran approximately the same risk of death due to melanoma of 3 per 100,000 as a U.S. resident during the period 1950 to 1969, and a 70-year-old Australian ran approximately the same risk of death due to other skin cancer of 4 per 100,000.

The total number of deaths recorded in the U.S. during the period of 1950 to 1969 for males and females due to malignant melanoma and other skin cancer is given in T. J. Mason et al.



Source: Lee and Carter, 1970.

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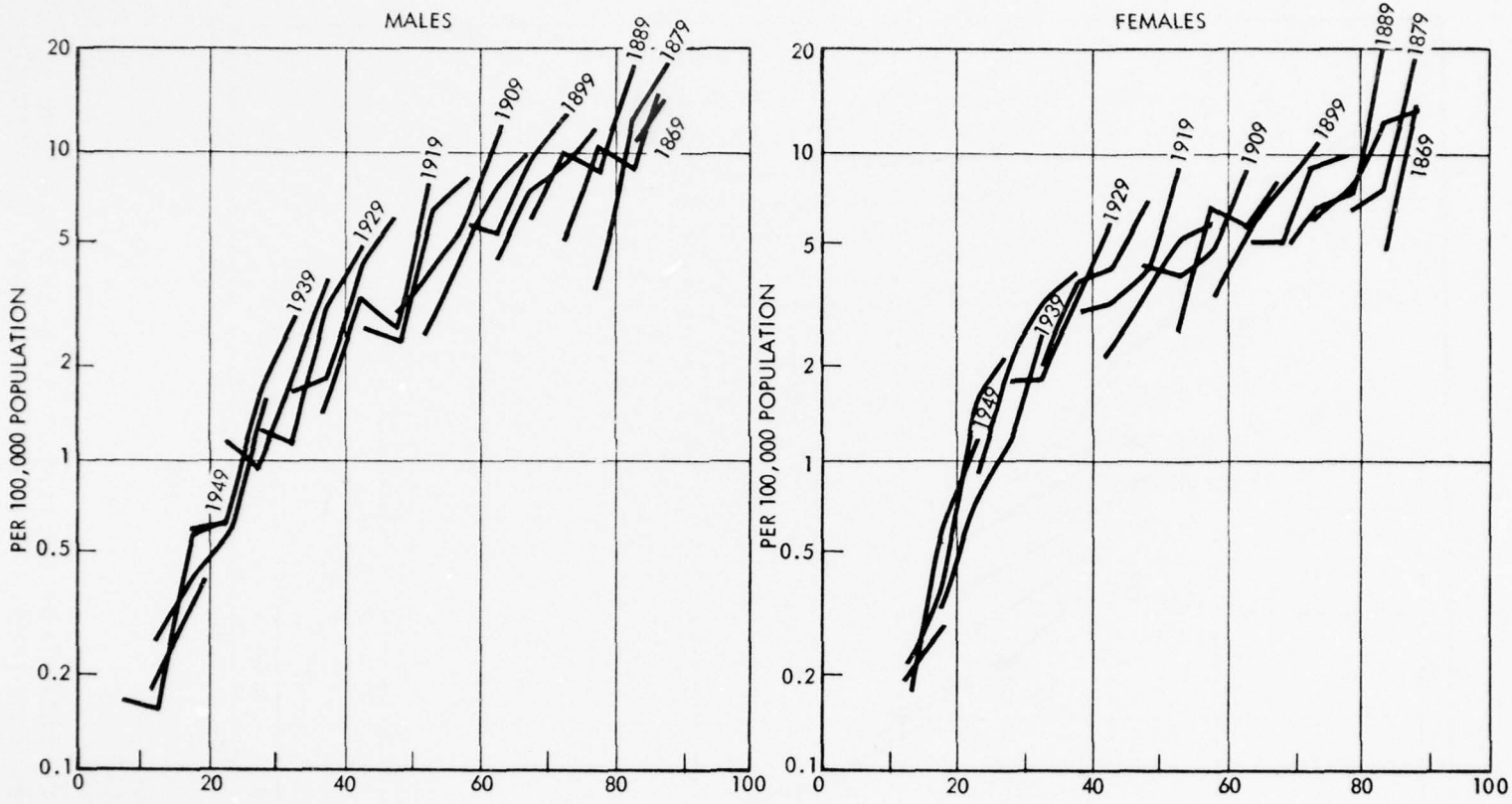
FIGURE 35. Death rate from malignant melanoma by birth cohort: sexes combined. England and Wales, 1951-1965.



Source: L. Teppo et al., 1975.

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FIGURE 36. Age-specific incidence rates (per 10^5) of cutaneous melanoma for 5-year birth cohorts based on the cross-sectional mean annual age-specific incidence rates in 1954-58, 1959-63, 1964-68 and 1969-73 in Finland, by sex. The mid-year of each birth cohort is indicated in the figure.

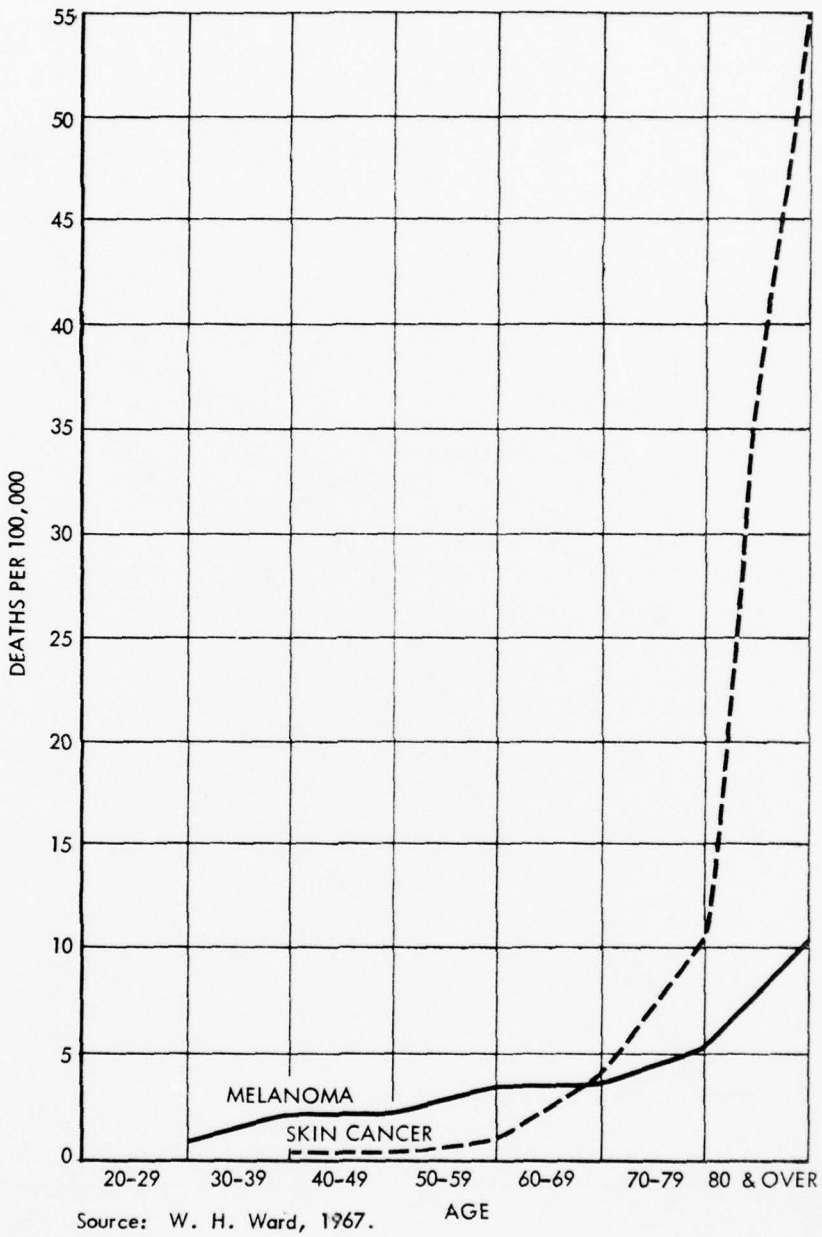
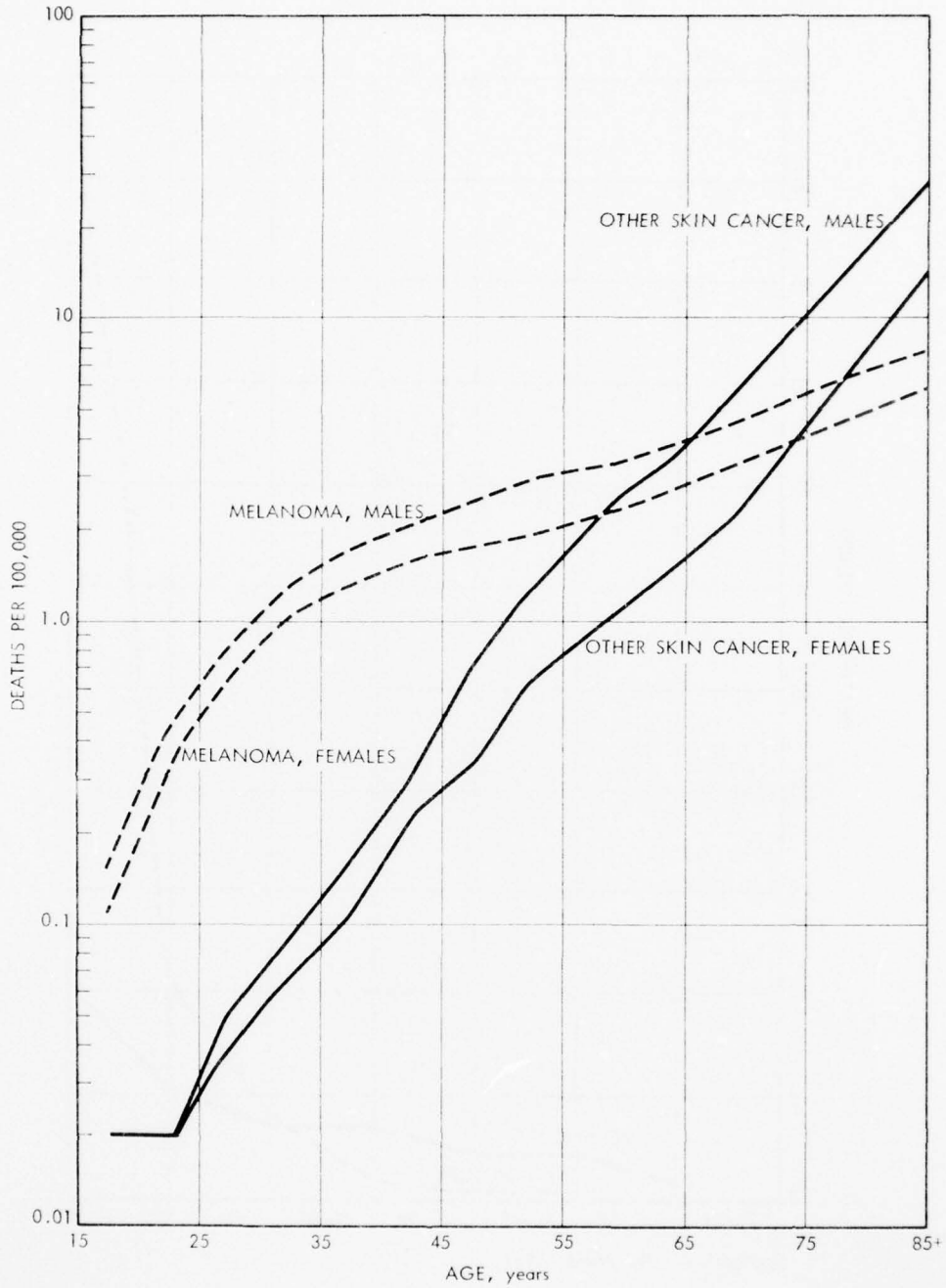


FIGURE 37. Deaths due to malignant melanoma and other skin cancers in 1955. Rate per million of population in each age group for Australia



Source: T. J. Mason et al., DHEW Publication No. (NIH) 75-780.

FIGURE 38. U.S. white mortality rates for malignant melanoma and other skin cancer, 1950-69

(Table 7). It is clear that even without consideration of the difference in the age distribution of deaths for the two types of skin tumor, malignant melanoma has been a more serious health problem in the United States. Since the death rate due to malignant melanoma has been rising and the death rate due to skin cancer has been falling, it can be expected that future data will indicate a much wider discrepancy in the number of deaths reported for the two types of tumors.

TABLE 7. NUMBER OF WHITE DEATHS IN U.S. DUE TO MALIGNANT MELANOMA AND OTHER SKIN CANCER, 1950 to 1969

	MALES	FEMALES
Malignant Melanoma	23,417	18,865
Other Skin Cancer	21,722	12,937

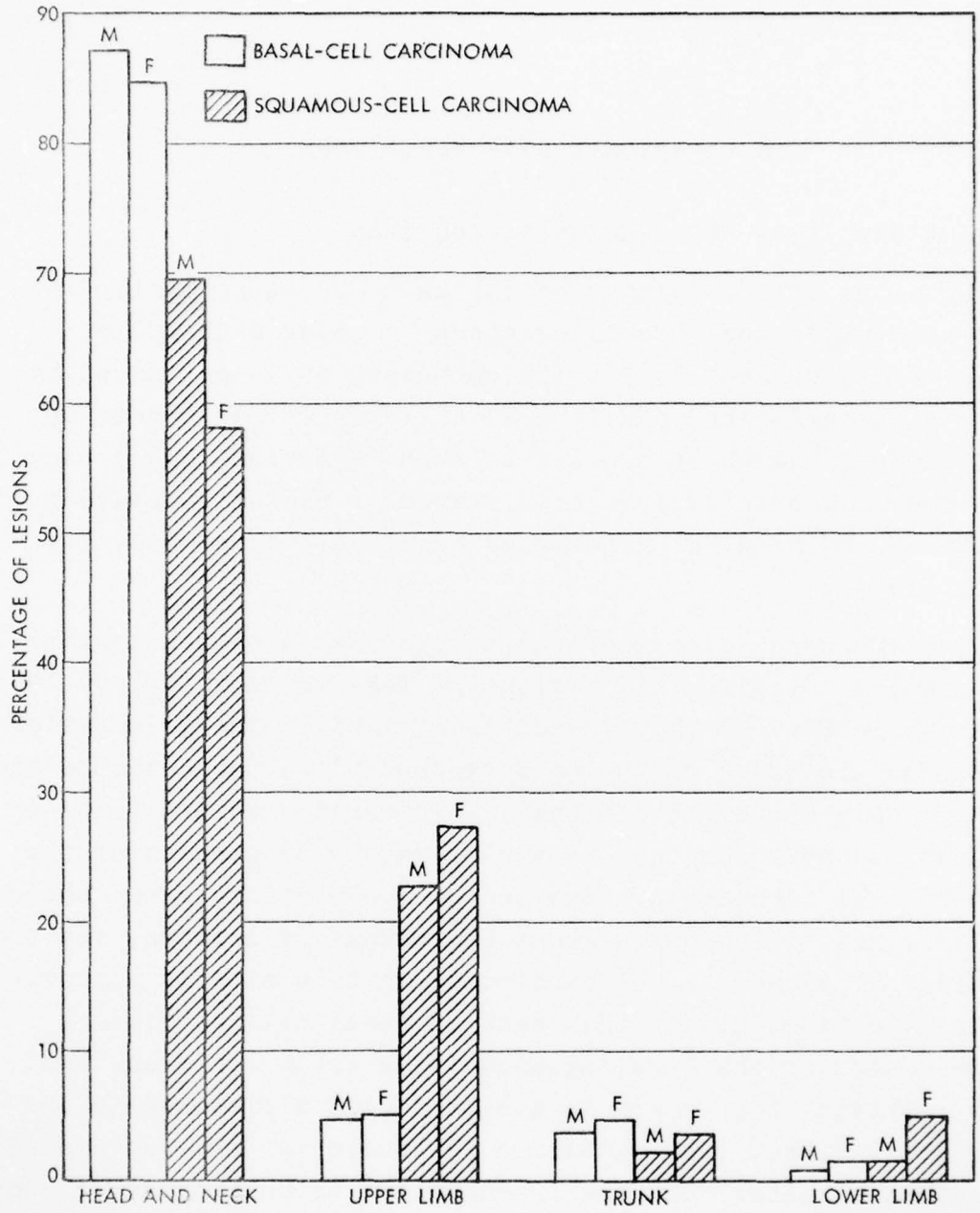
Maps of malignant melanoma and other skin cancer mortality for the U.S. white population, distributed by state economic area, are available for the period 1950 to 1969 (T. J. Mason et al.). These show that, in general, mortality from both types of skin cancer tend to be highest in the southeastern states. However, there are many state economic areas where other skin cancer incidence is significantly higher than the U.S. average and malignant melanoma incidence is not significantly different from the U.S. average and vice versa. Other mouth and throat cancer in females was also found to be highest in southeastern states, illustrating the point that a latitude gradient in cancer incidence is, by itself, insufficient evidence to implicate solar ultraviolet radiation as a causative factor.

5. ANATOMIC SITE VARIATIONS

5.1 ANATOMIC SITE FREQUENCY DISTRIBUTIONS

Squamous cell carcinoma of the skin occurs primarily on those skin sites most heavily exposed to solar ultraviolet radiation (F. Urbach, 1969). In contrast, it is estimated by Urbach that one-third of all basal cell carcinomas appear on areas normally slightly exposed to such radiation, suggesting that some factor in additon to ultraviolet radiation plays a significant role in the genesis of basal cell carcinoma (F. Urbach, 1969).

The frequency distributions of other skin cancer lesions by anatomical site for six regions of Texas during 1944 to 1966 are shown in Fig. 39 (E. J. Macdonald, 1975). The great majority of lesions are found on the most exposed site, the head and neck. Approximately 85 percent of basal cell carcinomas are found on the head and neck compared to approximately 65 percent of the squamous cell carcinomas. The second most exposed site, the upper limb, has the second highest percentage of lesions, but the frequency of squamous cell carcinomas in that site is approximately five times higher than that of basal cell carcinomas. The inversion of the basal/squamous risk ratio for these two sites indicates that there is a significant difference in the response to ultraviolet radiation for these two tumors, depending on anatomical site. The low frequencies for both types of tumors in the relatively unexposed sites, the trunk and lower limb, are consistent with the hypothesis that solar ultraviolet radiation is the most significant environmental factor in the genesis of these tumors. The low but significantly higher frequencies for the lower limb in females (presumably wearing nylon stockings)



Source: E. J. MacDonald, 1976.

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FIGURE 39. Distribution of other skin cancer lesions by anatomical site for six regions in Texas, 1944-1966.

as compared to males (presumably wearing relatively opaque trousers) is also consistent with the hypothesis.

The distribution of 5632 squamous cell carcinomas with respect to northern and southern Sweden is given in Table 8 (G. Swanbeck and L Hillström, 1971). The quotient between incidence rate in the northern and southern part of Sweden was found to be significantly higher for the head, hand, and lower limb. Paradoxically, 25 percent of the squamous cell carcinomas were found in the genital region which receives minimal solar ultraviolet radiation and was not even represented as a site category in the southern Texas data of Fig. 39. The finding that the incidence rate for the genital region was equal for the northern and southern parts of Sweden strongly suggests that a causative factor other than solar ultraviolet radiation was involved in the genesis of squamous cell carcinoma in that unexposed anatomic site.

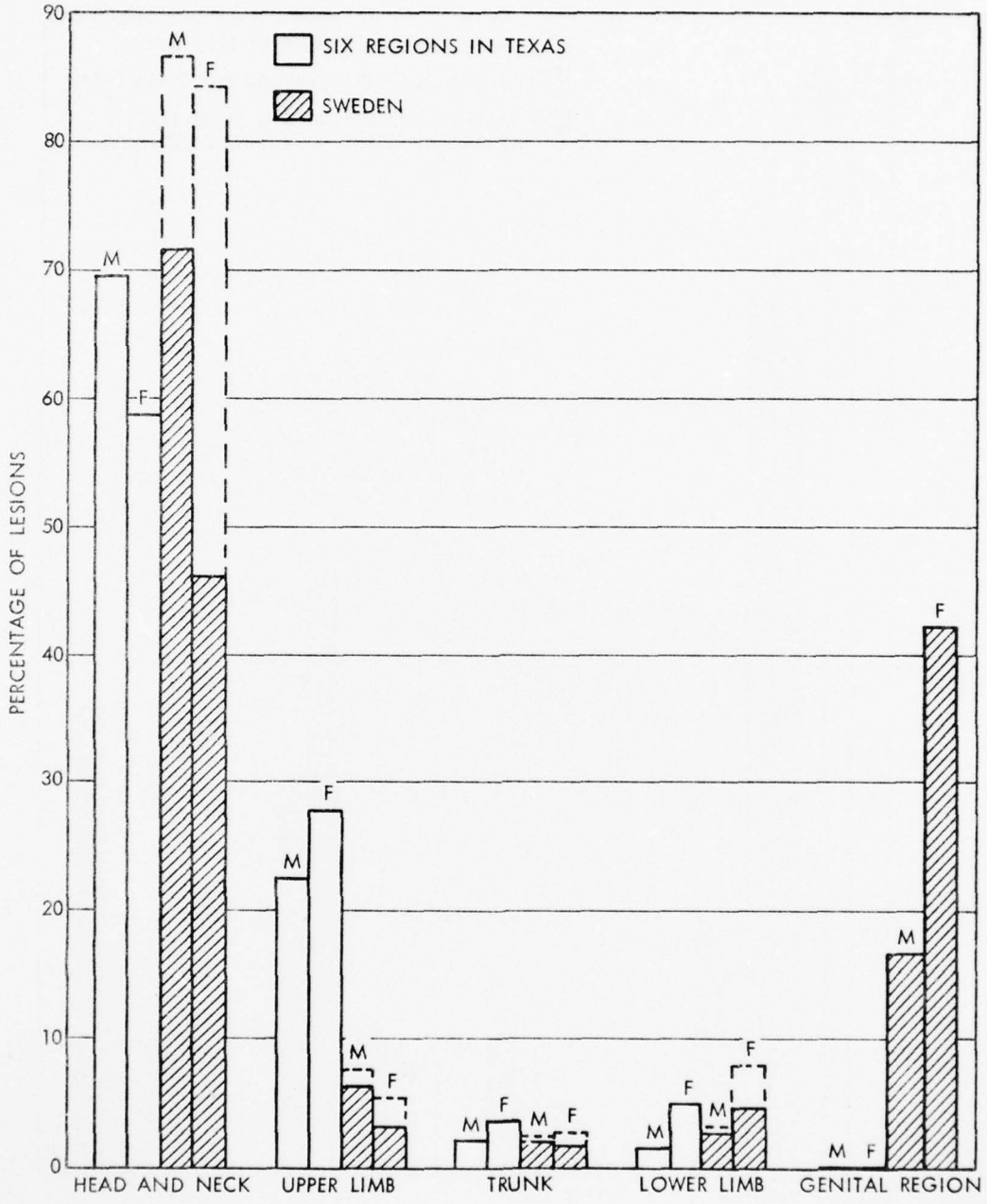
TABLE 8. DISTRIBUTION OF SQUAMOUS CELL CARCINOMAS OF DIFFERENT BODY REGIONS WITH RESPECT TO NORTHERN AND SOUTHERN PARTS OF SWEDEN

In 1963 19.8% of the population lived in the northern and 80.2% in the southern part of Sweden.

Location	Total Number of Patients	Percentage In		Quotient Between Incidence Rate in Southern and Northern Part	Statistically Significant Difference From Distribution of the Population
		Northern Part	Southern Part		
HEAD	3,819	14.6	85.4	1.44	Significant $p<0.001$
HAND	129	6.2	93.8	3.74	Significant $p<0.001$
LOWER LIMB	143	12.6	37.4	1.71	Significant $p<0.05$
TRUNK	100	16.0	84.0	1.30	Not significant
GENITALS	1,416	20.0	80.0	0.99	Not significant
ARM	25	24.0	76.0	0.78	Not significant
TOTAL	5,632				

In Fig. 40, the squamous cell site frequency data for southern Texas in Fig. 39 is compared with that for Sweden (G. Swanbeck and L. Hillström, 1971). In Swedish females, 42 percent of squamous cell carcinomas were found in the genital region, and 16.5 percent in Swedish males. In order to properly compare the Swedish site frequency distribution with that of southern Texas, the carcinomas in the genital region should be excluded. The resulting adjusted site frequency distributions are indicated in Fig. 40 by the dashed lines. The comparison in the squamous cell site frequency distributions for Sweden, lying at a latitude above 60° N, and southern Texas, almost 30° closer to the equator, shows a significant change in site frequency distributions. The head and neck frequency decreased appreciably for both sexes with decreased latitude, upper limb frequency increased by a factor of three for males and five for females, trunk frequency remained virtually unchanged, and lower limb frequency decreased approximately 40 percent in females and 50 percent in males. Such a redistribution of anatomic site frequencies is not inconsistent with the hypothesis associating solar ultraviolet radiation with squamous cell carcinoma, since the relative solar exposure of the sites must certainly change significantly with latitude and each site incidence will lie on a different part of a different site-specific dose response curve.

In Fig. 41 the frequency distributions by site in Finland are shown for basal cell carcinoma, squamous cell carcinoma, and malignant melanoma (L. Teppo et al.). As expected, the head and neck was again the site of the great majority of basal and squamous cell carcinomas, but less than 20 percent of malignant melanomas were located on this most exposed site. On the trunk, the least exposed site, was anomalously found 48 percent of the male and 28 percent of the female malignant melanoma tumors, compared to approximately 10 percent for both sexes for squamous and basal cell carcinomas.



Sources: E. J. MacDonald, 1976; G. Swanbeck and L. Hillström, 1971.

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FIGURE 40. Distribution of squamous cell carcinomas by anatomical site for six regions in Texas and Sweden.

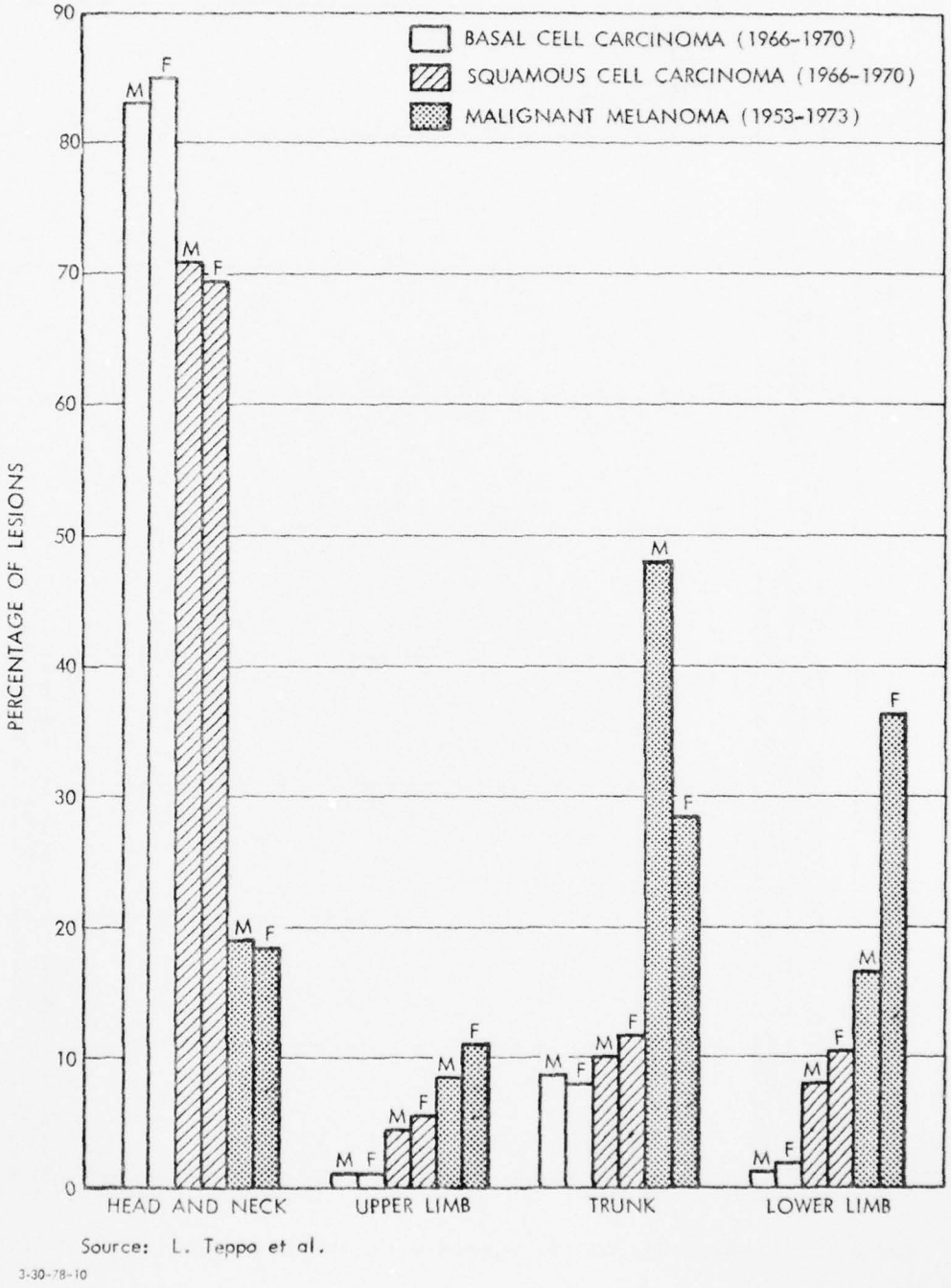

FIGURE 41. Distribution of skin cancer, by anatomical site, in Finland

The high frequency (36 percent in Finland) of malignant melanoma in the lower limb for females is one of the chief arguments advanced by the proponents of the ultraviolet hypothesis for malignant melanoma. However, if one accepts the hypothesis that the lower limb of females is more sensitive to solar ultraviolet radiation than the other three sites without dominating them, as the head and neck dominates in other skin cancer, one would expect that the frequency of tumors of the lower limb would be higher relative to the other sites in an environment of higher solar radiation. This is evidently not the case. The frequency distributions by anatomic site are shown in Fig. 42 for southern Texas (E. J. Macdonald, 1976) and Finland (L. Teppo) for the periods 1944-66 and 1953-73, respectively. The frequency for the lower limb in females was only 28 percent in southern Texas compared to 36 percent in Finland. The frequency for the relatively unexposed trunk in males also drops from 48 percent in Finland to 25 percent in southern Texas. However, these differences are probably not as large as indicated because the average time period for the Finland data was 1963, whereas for the southern Texas data it was 1955. In Section 5.3 it is shown that the frequencies at these anatomic sites have been increasing sharply with time. Incidence of malignant melanoma of the trunk in males has tripled between 1953 to 1959 and 1971 to 1973 in Finland and incidence in the lower limb in females has doubled (see Fig. 49). If corrections for the time displacement are made in Fig. 42, it appears that the frequency distribution for malignant melanoma by anatomic site may be close to being independent of latitude. To further investigate this possibility, a comparison (Fig. 43) was made of the anatomic site distributions of 400 malignant melanoma tumors for the period 1963 to 1965 in Queensland, Australia (N. C. Davis et al., 1966), 54 percent of which lies within the tropical zone, with those in Finland (L. Teppo et al.) for the period 1953 to 1973. These two regions represent the extremes of solar ultraviolet radiation

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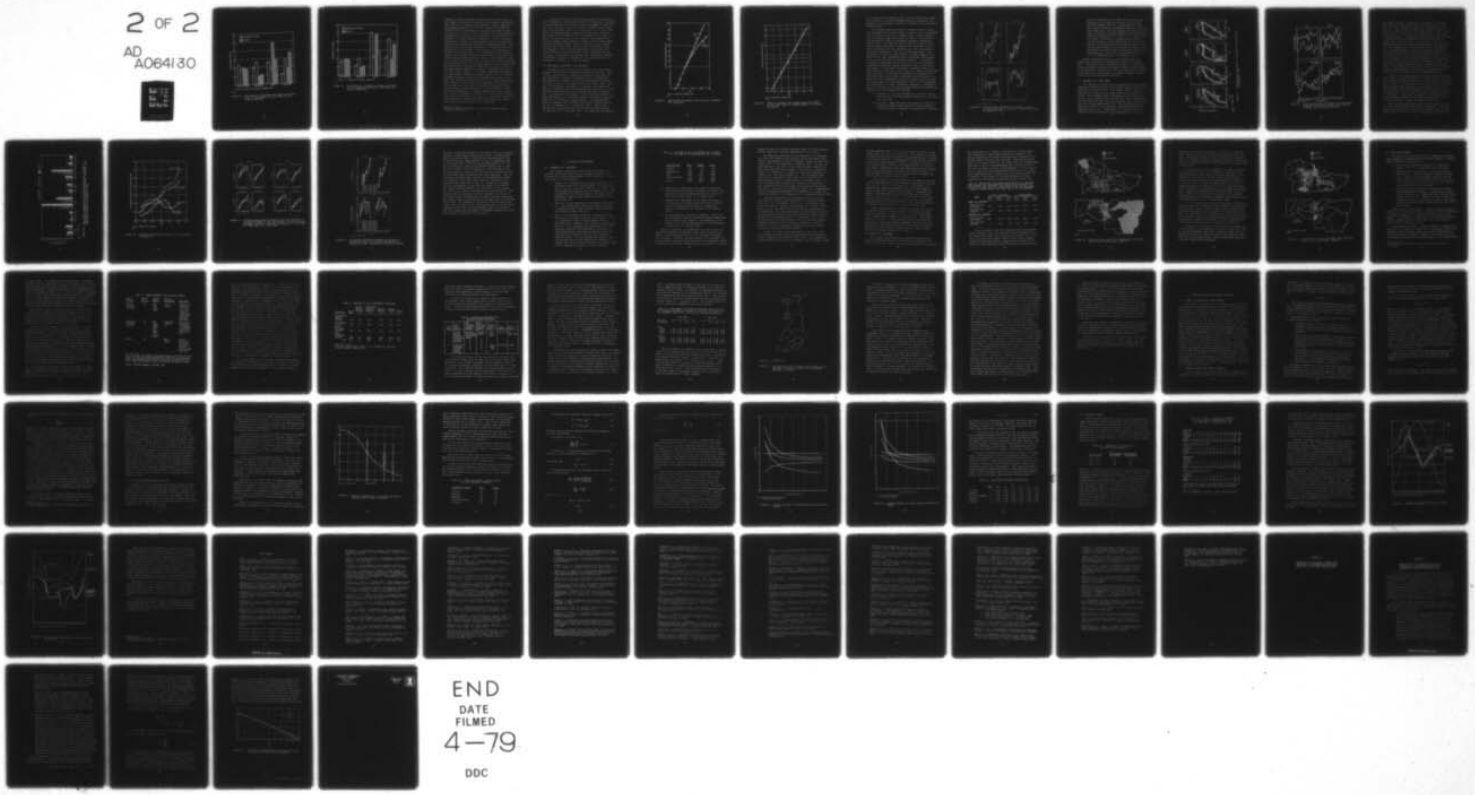

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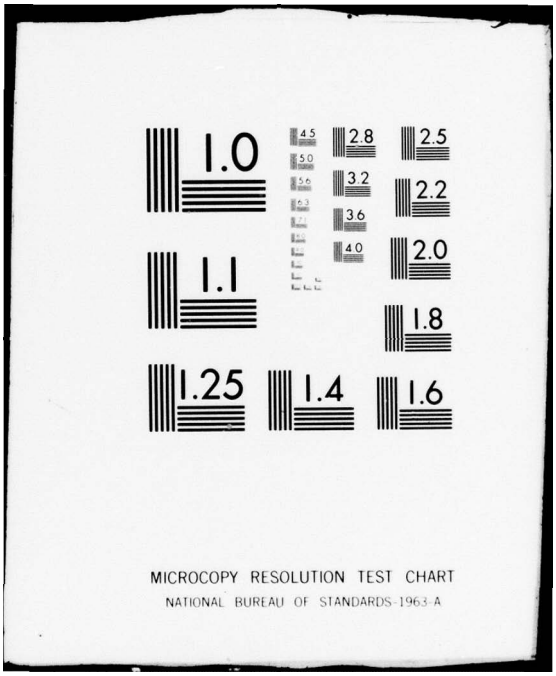
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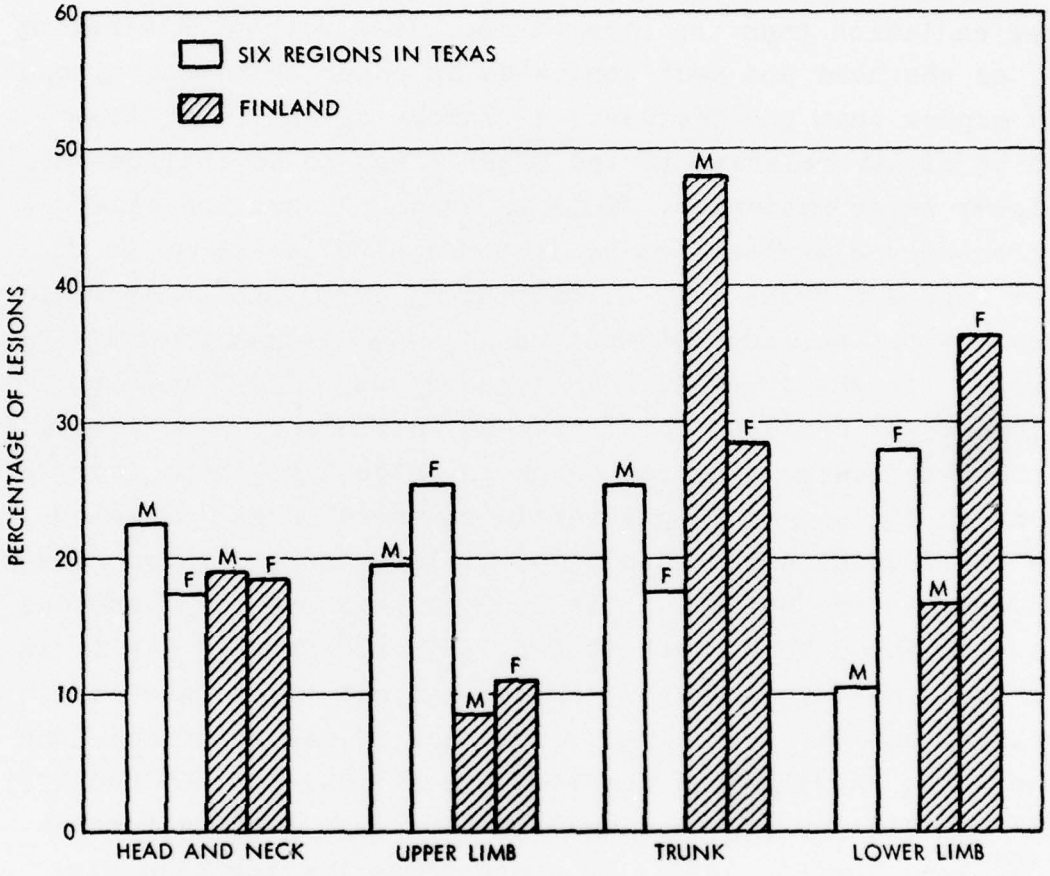

Sources: L. Teppo et al. 1975 and E. J. MacDonald, 1976.

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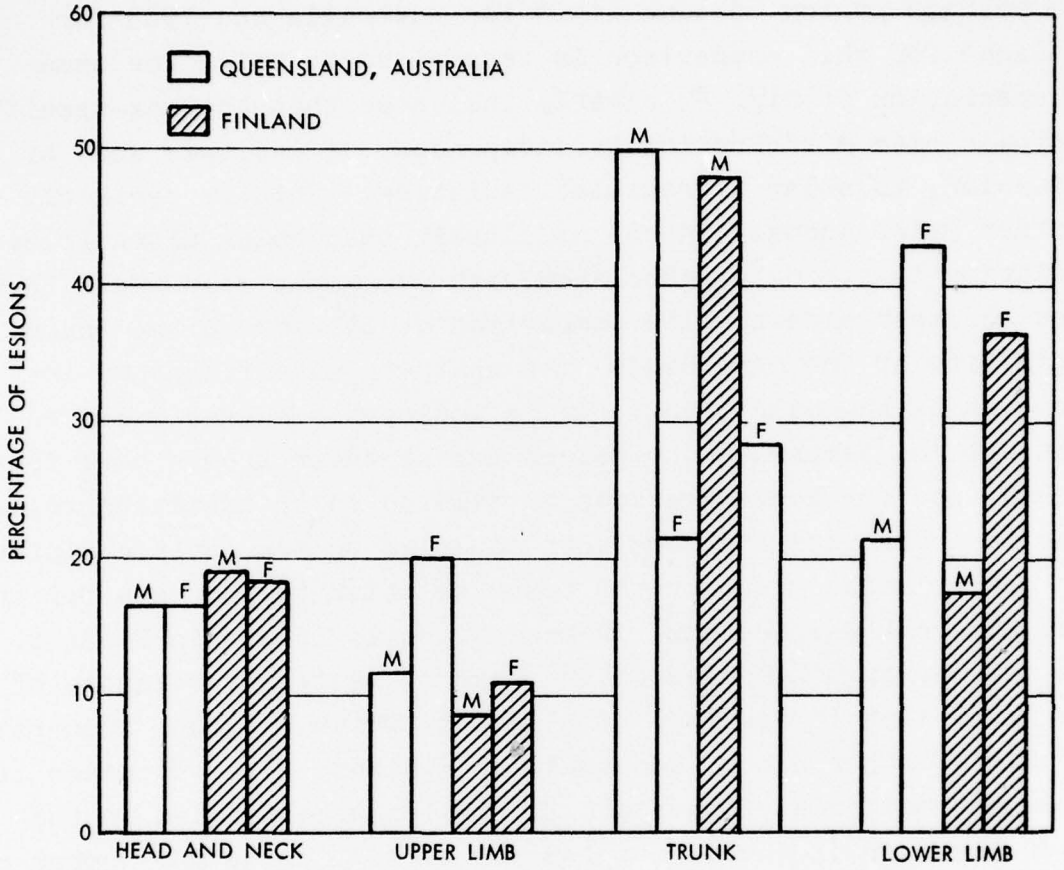
FIGURE 42. Distribution of malignant melanoma, by anatomic site, in six regions of Texas (1944-66) and Finland (1953-73)



Sources: N. C. Davis et al., 1966 and L. Teppo et al.

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FIGURE 43. Distribution of malignant melanoma by anatomic site in Queensland Australia (1963-1965) and Finland (1953-1973)

exposure in which Caucasian populations live, and if there is any change in sex-specific anatomic site frequency distribution with latitude, it should be most apparent in this comparison. The average period of time (1964 for Australia and 1963 for Finland) for this comparison is very close to being the same. An inspection of Fig. 43 clearly indicates that the sex-specific anatomic site distribution is independent of latitude and, by extension, to solar ultraviolet radiation. This is certainly another major anomaly in the hypothesis that solar ultraviolet radiation is strongly associated with malignant melanoma. Perhaps the best site-to-site comparison to illustrate the incompatibility of the hypothesis with anatomic site frequency invariance is the male trunk. It is indisputable that males in tropical and temperate Queensland expose their trunks more frequently and for longer periods of time to solar radiation relative to their head and neck than do males in near arctic Finland. Yet the melanoma risk for the trunk relative to the risk for the head and neck was the same in Queensland as it was in Finland. The same argument applies to the case of malignant melanoma of the lower limb in females. In Iceland, which has cool summers and lies farther north than southern Finland, 24 of 48 cases of malignant melanoma of the skin in females were located in the lower limb during the period 1955 to 1974.* While the number of these Icelandic cases is small, the agreement in frequency for this anatomic site with that in Finland and Queensland lends further support to the invariance of the distribution of anatomic site frequencies. A sub-site anomaly is the fact that of the 24 cases of malignant melanoma of the lower limb in females. seven were located in the foot, which is very rarely exposed to solar radiation in Iceland and which constitutes but a small fraction of the surface area of the lower limb.

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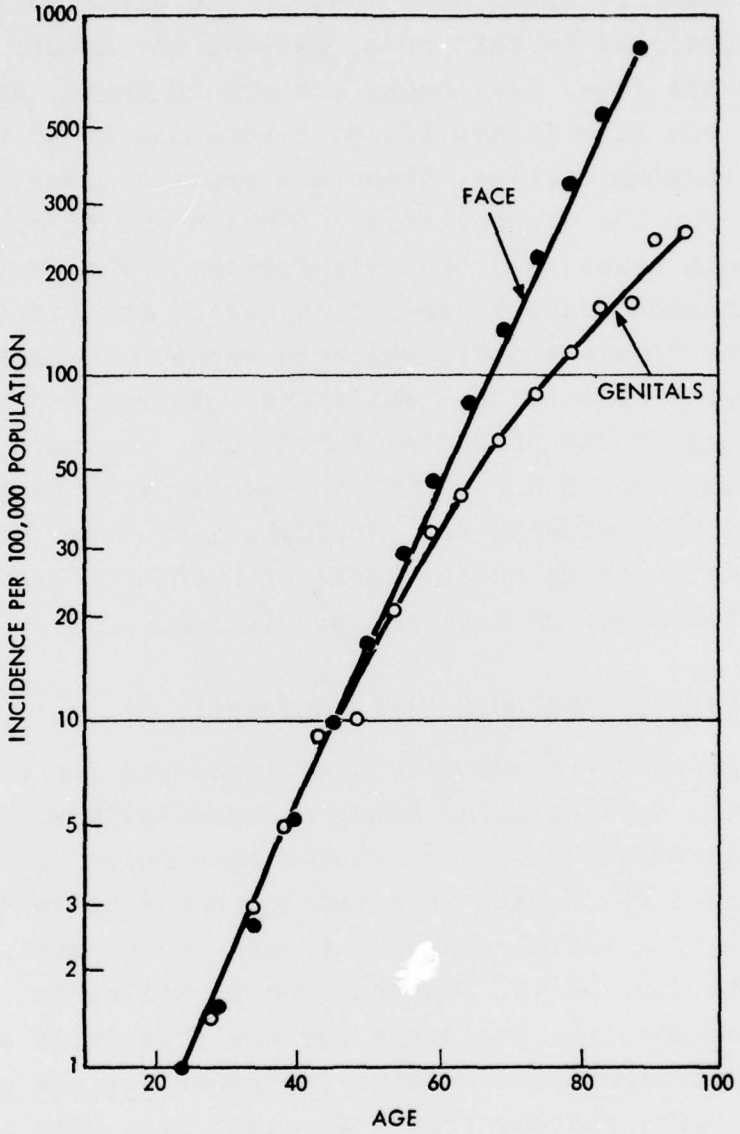
*Personal communication with H. Tulinius, Icelandic Cancer Registry, November 1977.

It has been reported, for a Queensland 1963 to 1969 series that the number of cases observed, if the distribution is assumed to be proportional to skin area, exceeds the number of cases expected for the face, leg, neck, and arm in women, and the face, ear, neck, and back in men (J. M. Elwood and J. A. H. Lee, 1975). While, in varying degrees, these are exposed areas, deficits were found for the exposed areas of the hands of both sexes, the chest of both sexes, and the male forearm. The frequency for the male abdomen, rarely exposed in males, was six times higher than for the female abdomen which is exposed in those females wearing bikini swim suits. While the male ear had four times the frequency of the protected female ear, the partially protected female neck had a 50 percent higher frequency than the male neck. The evidence for linking solar ultraviolet radiation to malignant melanoma on the basis of such unit body area calculations is therefore not very convincing.

5.2 AGE-SPECIFIC ANATOMIC SITE INCIDENCE

The age-specific anatomic site incidence for solar-caused squamous cell carcinoma increases exponentially with age. This is best illustrated in a homogeneous population which has not been subjected to changes in composition due to immigration. The age-specific incidence for the face and genitals in Sweden are shown in Fig. 44 (G. Swanbeck and L. Hillström, 1971). Note that the age-specific incidence for the face falls almost exactly on a straight line on semi-log paper but the curve for the genitals departs sharply from a straight line with increasing age. This departure adds support to the conclusion (Section 5.1) that the squamous cell carcinomas found in the genital region in Sweden are not related to solar radiation. The age-specific curve for squamous cell carcinoma of the lower limb is shown in Fig. 45 (G. Swanbeck and L. Hillström, 1969). Similar age-specific rate curves was found for the arm and hand, and head (G. Swanbeck and L. Hillström, 1970). The shape and the sameness



Source: Swannbeck and Hillström, 1971.

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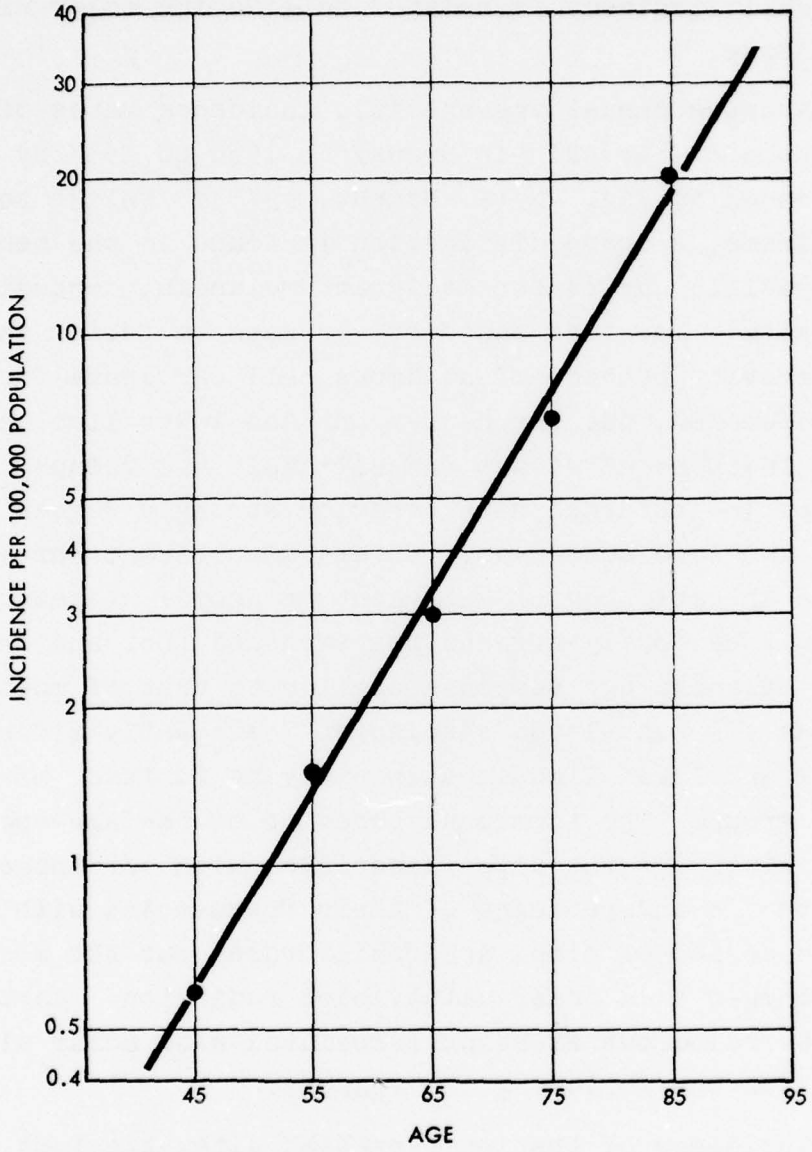
FIGURE 44. Age-specific incidence rate curves for squamous cell carcinoma



Source: Swannbeck and Hillström, 1969.

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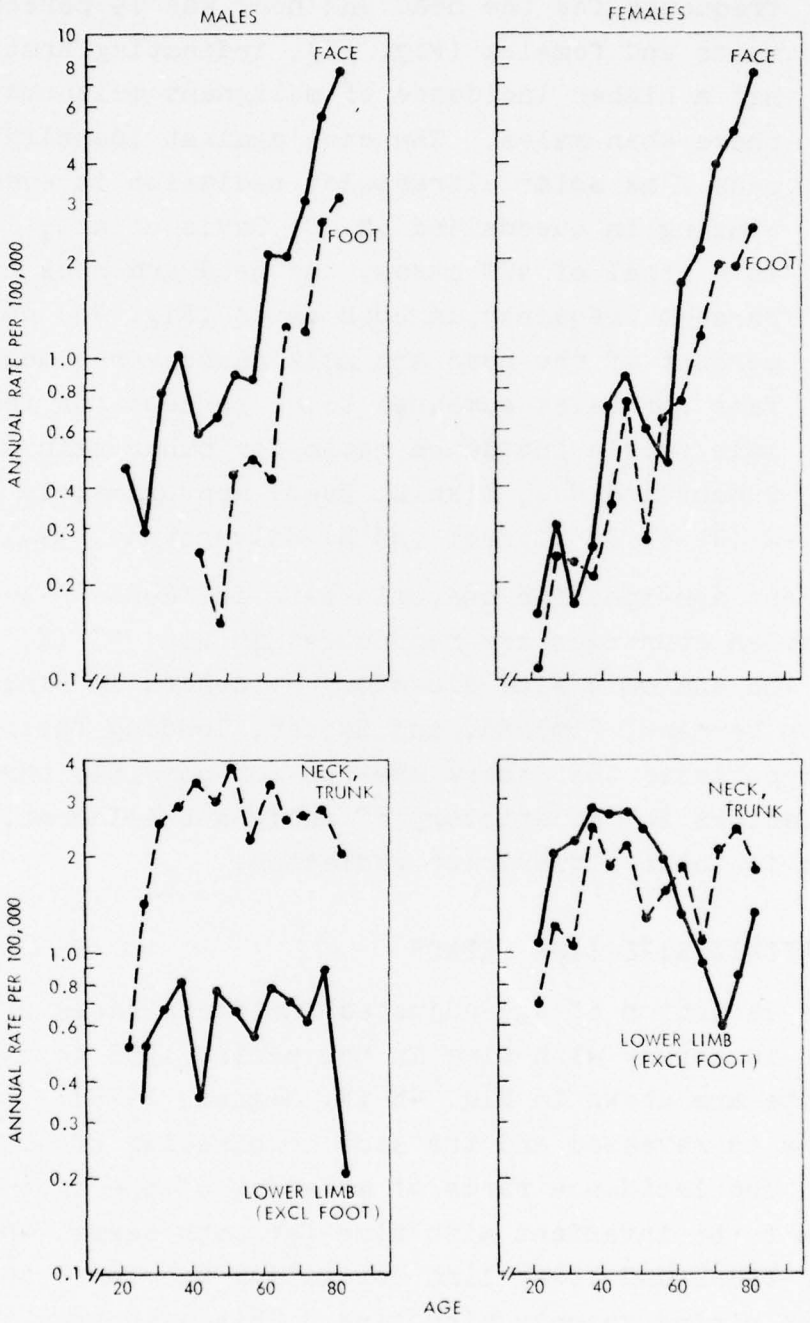
FIGURE 45. Number of squamous cell cancer cases with tumors on the lower limbs per 100,000 people in different age groups

in the shape of the incidence rate curves for the various sites are therefore in excellent agreement with the hypothesis that squamous cell carcinoma is related to lifetime solar ultraviolet radiation dose.

The average annual age-specific incidence rates of malignant melanoma of the skin in Norway in 1955 to 1957 by anatomical site are shown in Fig. 46 (K. Magnus, 1975). Unlike squamous cell carcinoma, a sharp distinction is found in the behavior of the age-specific curves for malignant melanoma, depending on anatomic site. The face and foot are seen to follow the exponential behavior pattern of squamous cell carcinoma for both males and females, but the neck-trunk and lower limb appear to be almost independent of age for all adult age groups. This discrepancy in incidence rate behavior strongly suggests that there are two (and conceivably three) significant carcinogenic factors in the etiology of malignant melanoma. A postulated carcinogen X evidently affects the face and foot and induces a malignant melanoma age response similar to that of most other carcinogens. A postulated carcinogen Y evidently affects the neck-trunk and lower limb in such a way as to favor no particular adult age group. The anomalous behavior of the age-specific incidence rates for the sites associated with carcinogen Y, together with the independence of their frequencies with latitude at a given period of time, apparently rules out the possibility that carcinogen Y is solar ultraviolet radiation. Carcinogen X can also be ruled out as being associated with solar ultraviolet radiation for the following two reasons:

(1) incidence of the least exposed site, the foot, was almost as high as the most heavily exposed site, the face (Fig. 46). and

(2) in El Paso, where the other skin cancer sex ratio of 2 indicates a heavy excess exposure of solar radiation in males relative to females, the male/female incidence



Source: K. Magnus, 1975.

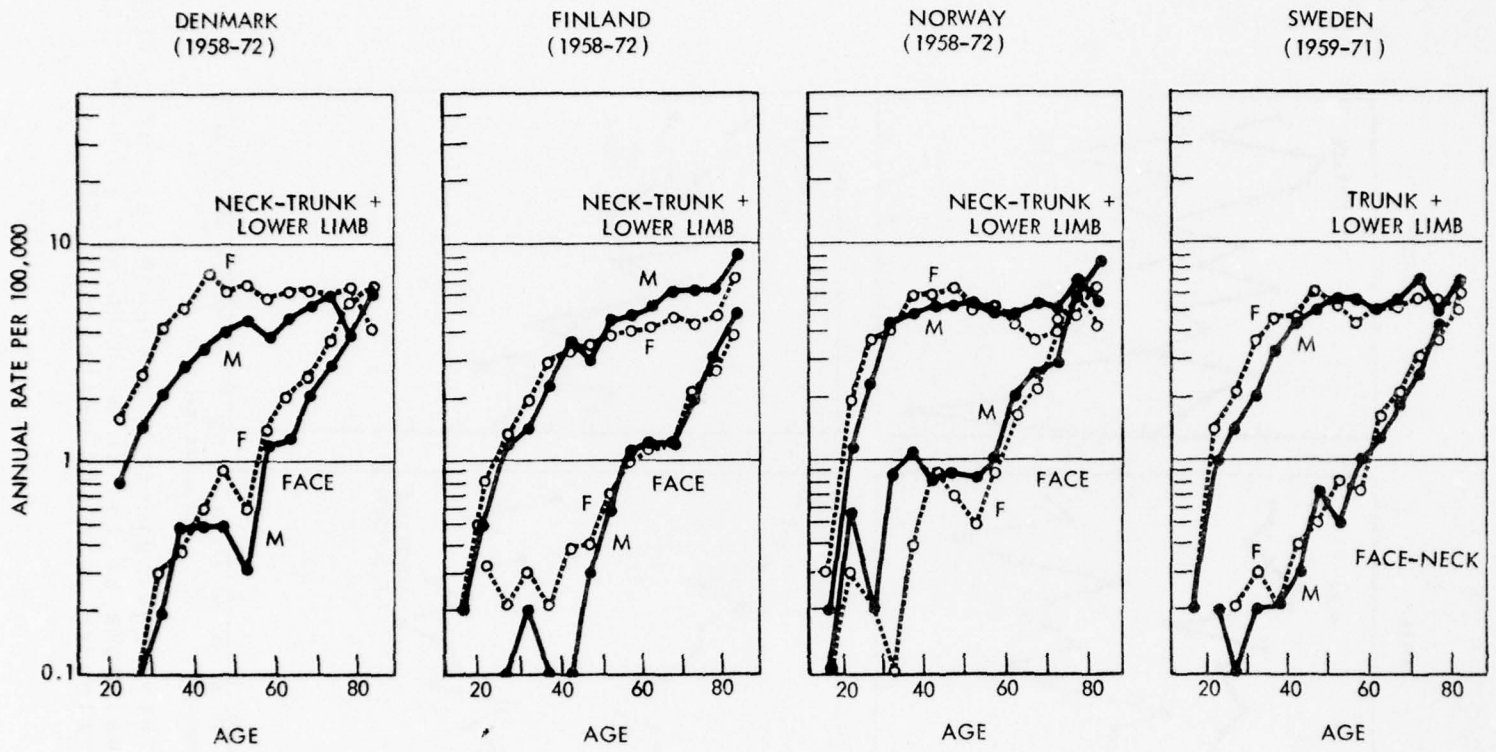
FIGURE 46. Average annual age-specific incidence rates of malignant melanoma of the skin in Norway 1955-1970 by anatomical site.

ratio for melanoma was 0.8 (Fig. 9) and the anatomic frequency for the head and neck was 19 percent for males and females (Fig. 42), indicating that females had a higher incidence of malignant melanoma of the face there than males. The case against identifying carcinogen X as solar ultraviolet radiation is even more convincing in Queensland (N. C. Davis et al., 1966) where, in a total of 400 cases, the head and neck had a 17 percent frequency in both sexes (Fig. 43) but only 48 percent of the head and neck cases were located in the face for males compared to 61 percent for females. The male/female incidence ratio for other skin cancer in Queensland was, like El Paso, approximately equal to 2 (G. G. Carmichael and H. Silverstone, 1961).

Recent age-specific anatomic site incidence rates for Scandinavian countries are reproduced in Fig. 47 (K. Magnus 1977). The anatomic site dichotomy evidenced in Finland also exists in Denmark, Finland, and Sweden, lending further support to the hypothesis that there are two (or possibly three) significant factors in the etiology of malignant melanoma, neither of which is solar ultraviolet radiation.

5.3 ANATOMIC SITE TIME TRENDS

The variation of age-adjusted incidence rates of malignant melanoma in Norway with time in the period 1955 to 1970 by anatomic site are shown in Fig. 48 (K. Magnus, 1975). Another dichotomy is revealed and the same combination of sites is involved. The incidence rates of melanoma of the face and foot are seen to be invariant with time for both sexes, whereas for the neck-trunk and lower limb (excluding the foot) the incidence rates are rising sharply with time. This dichotomy adds yet additional support to the two-factor etiology hypothesis discussed in Section 5.2. Furthermore, Fig. 48 reveals some information about differences in the time behavior of the two



Source: K. Magnus, 1977.

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FIGURE 47. Average annual age-specific incidence rate according to anatomical site.

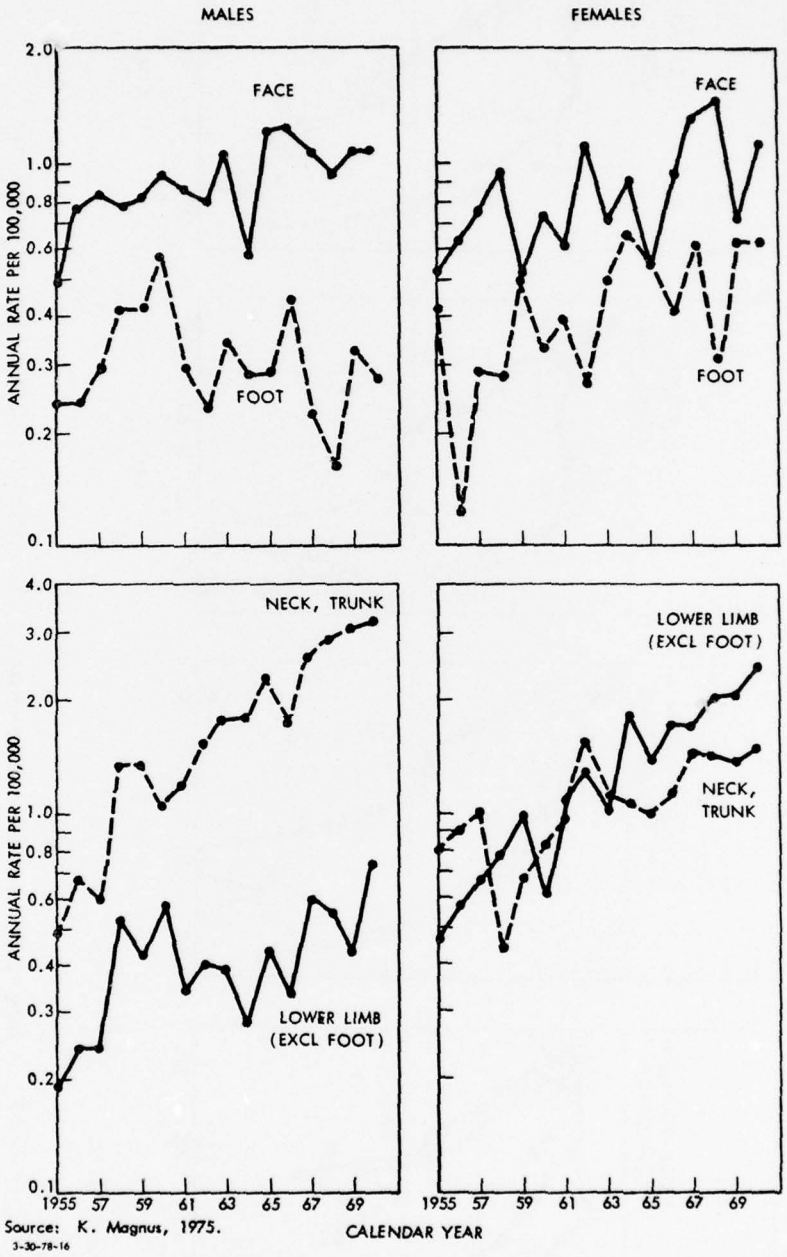


FIGURE 48. Total age-adjusted incidence rate of malignant melanoma of the skin in Norway 1955-1970 by calendar year and anatomical site.

carcinogenic factors. Apparently, carcinogen X is invariant with time, while carcinogen Y has been increasing at a rapid rate with time. Analogous anatomic site incidence data for Finland (L. Teppo et al.) for the periods 1953 to 1959, 1961 to 1970, and 1971 to 1973 (Fig. 49) follow the same time trends observed in Norway. Crossing the Atlantic ocean, this difference in anatomic site time variation has also been observed in Connecticut, as shown in Fig. 50. Incidence in the face remained essentially stationary, whereas incidence in the trunk more than quadrupled in a three-decade period. Carcinogen Y, if it is assumed there are only two significant factors, is evidently more effective in producing malignant melanomas in the trunks of males and in the lower limbs of females. An alternative hypothesis is one in which carcinogen Y is responsible for the increase in the incidence of malignant melanoma of the trunk and a third carcinogen Z for the increase of the lower limbs. Carcinogen X may be related to genetic factors but carcinogen Y (and possible Z) must clearly involve some agent(s) whose worldwide toxicity has been increasing with time.

In Fig. 51 are reproduced the truncated age-adjusted incidence rates of malignant melanoma in four age groups by anatomic site in Finland for the periods 1953 to 1959, 1961 to 1970, and 1971 to 1973. The data parallel fairly well the data for Norway. There is additional information in the behavior of the upper limb incidence rates which evidently follow that for the trunk and lower limb, i.e., the upper limb may be primarily affected by carcinogen Y rather than carcinogen X. The curves of Fig. 51 are relatively noisy for the upper limb because of the relatively small number of cases occurring in that site.

The dichotomy between incidence in the face and foot and the neck-trunk and lower limb is also illustrated in the birth cohort curves for Norway in Fig. 52 (K. Magnus, 1975) for the period 1955 to 1970. For the neck-trunk and lower limb there

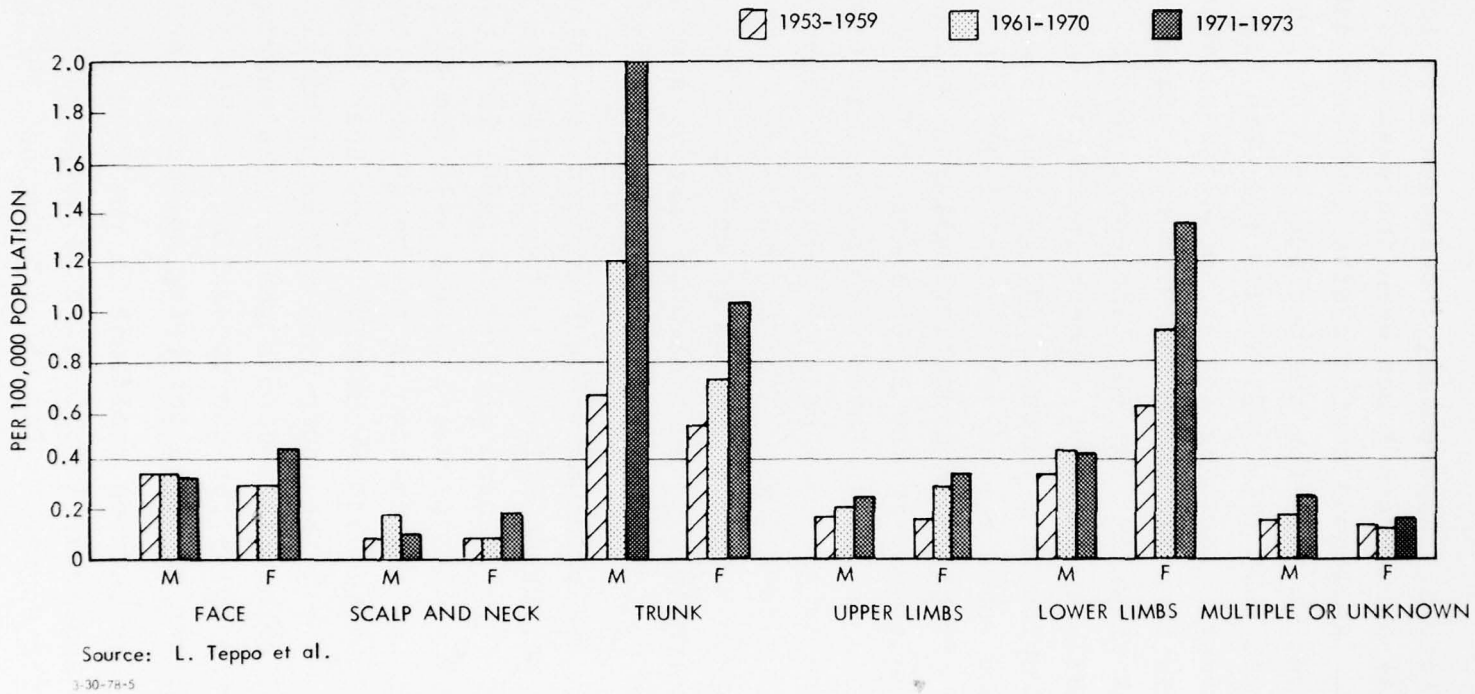
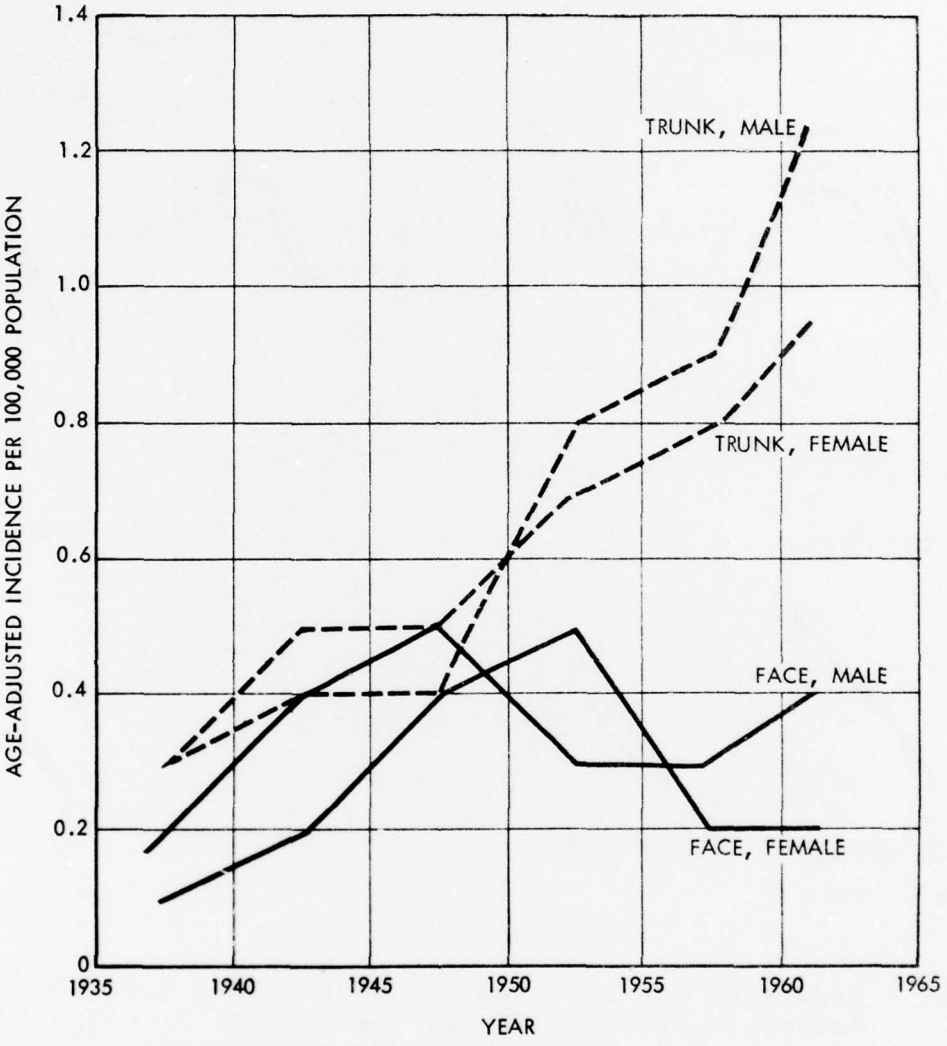


FIGURE 49. Mean annual age-adjusted incidence rates (per 100,000) of cutaneous melanoma in Finland in 1953-1959, 1961-1970, and 1971-1973, by sex and anatomical site



Source: Connecticut Tumor Registry.

3-30-78-15

FIGURE 50. Incidence of malignant melanoma of face and trunk in Connecticut

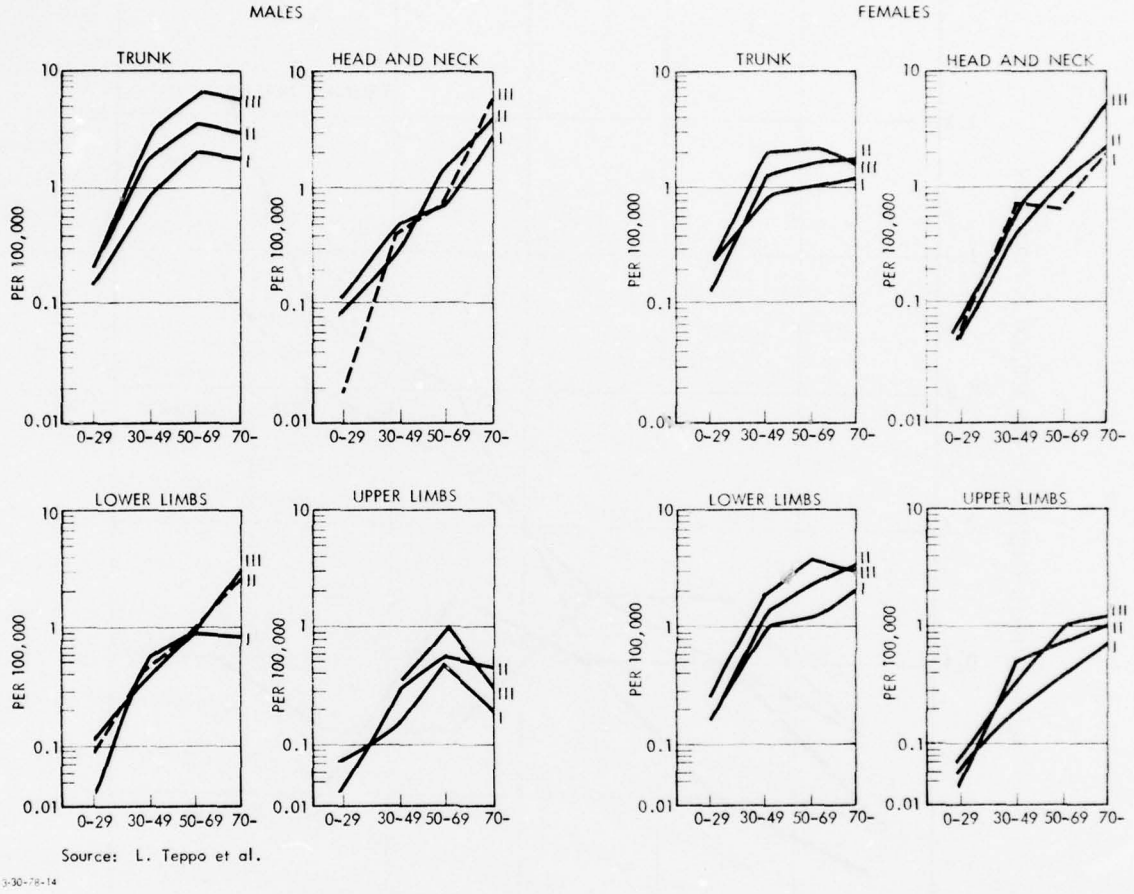
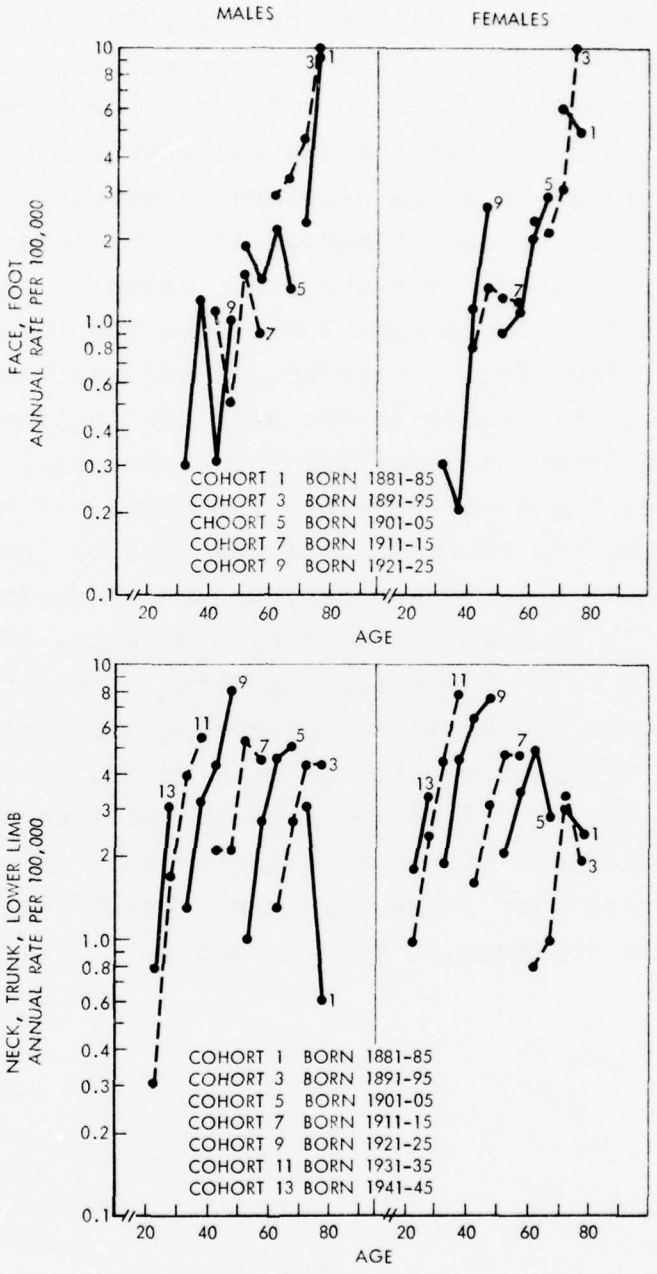


FIGURE 51. Truncated age-adjusted incidence rates (per 100,000) of cutaneous melanoma in four age-groups in Finland, by sex, anatomical location, and time of diagnosis (I = 1953-1959, II = 1961-1970, III = 1971-1973).



Source: K. Magnus, 1975.

3-30-78-21

FIGURE 52. Incidence of malignant melanoma of the skin in Norway 1955-1970 for selected combinations of anatomical sites. Age-specific rates for cohorts.

has been a relentless decrease in the age at which the incidence exceeds a certain value, say two per 100,000. For Norwegians born in the period 1881 to 1885 the age corresponding to this incidence value was approximately 70, and for Norwegians born in the period 1941 to 1945 the age was approximately 25. The rate of decrease in this age decelerated between 1931 to 1935 and 1941 to 1945. No such behavior is to be observed in Fig. 52 for incidence in the face and foot, which is consistent with the hypothesis that carcinogen X has been stationary. Most interesting and significant, however, is the additional information revealed by the birth cohort data for incidence of the neck-trunk and lower limb in Fig. 52. Evidently, carcinogen Y has been increasingly active since the decade of the 1880's. Its origin therefore dates all the way back to the Victorian era, and not to a more recent period such as World War II. The latter period is frequently cited by proponents of the solar ultraviolet radiation hypothesis as being associated with a sudden change in the clothing and solar exposure habits of Caucasian populations. The slowdown in the rate at which the birth rate cohort curves in Fig. 52 for neck-trunk and lower limb are being displaced to the left with age indicates that it is unlikely that the observed past increases in malignant melanoma for adults will be seen in children in future years.

6. ETIOLOGY OF SKIN CANCER

6.1 SQUAMOUS CELL CARCINOMA

The evidence identifying solar ultraviolet radiation as the most significant factor in the etiology of squamous cell carcinoma in Caucasian populations is very convincing. It consists mainly of the following:

1. Squamous cell carcinoma occurs almost exclusively in anatomical sites that receive maximal UV irradiation, such as the rim of the ear (Urbach et al., 1966). They are distributed primarily over the head and neck, and secondarily in the exposed areas of the upper limbs in geographic regions of high isolation such as El Paso, Texas (Fig. 39).

2. There is a strong dependence of incidence on latitude, e.g., the statistically significant higher incidence of exposed anatomic sites in southern Sweden compared with northern Sweden (Table 8).

3. There is a much higher incidence on exposed anatomic sites and in those who spend more time outdoors. This is illustrated in Table 9 by the Swedish data (L. Hillström and G. Swanbeck, 1970) showing a male/female ratio of 1.7 for squamous cell carcinomas of the head. The major reason for the difference in incidence between Swedish males and females evidently can be attributed to the protection by hair and clothing of high-risk sites. For the external ear, which is usually protected from solar radiation by long hair in females, the ratio of cases is equal to a striking value of 8.8, compared to a ratio of 1.1 for the face.

TABLE 9. DISTRIBUTION OF THE SQUAMOUS CELL CANCERS ON THE HEAD BY LOCALIZATION AND SEX IN SWEDEN

Localization	Male	Female	Total
Eyelids	104	74	178
External ear	842	96	938
Face	1258	1140	2398
Scalp and neck	195	110	305
Total	2399	1420	3819

4. Squamous cell carcinomas occur rarely in pigmented races whose skin is highly resistant to UV penetration and they are usually associated with old burns, lip scars, or chronic ulcers (E. A. Emmett 1973).

5. Squamous cell carcinomas can be readily produced in the laboratory in rodents with ultraviolet radiation to the exclusion of other types of malignancies (Epstein and Epstein, 1963; Epstein, 1965; Forbes, 1974).

6. DNA is damaged by ultraviolet radiation. Those with the recessively inherited disease xeroderma pigmentosum have a defect in the repair of DNA damaged by UV radiation and a strong predisposition to the development of skin cancer (C. Keeler, 1963).

There are apparently no anomalies to be found in the literature challenging the hypothesis that solar ultraviolet radiation is the dominating factor in the etiology of squamous cell carcinoma. However, the high incidence in the genital region in Sweden illustrates the possibility of etiological factors extraneous to ultraviolet radiation which may prevail in a given

region and which may inflate incidence values for solar-exposure related tumors in a complete registration of all tumors.

The dominating importance of sun-radiation as an etiological factor for squamous cell carcinoma in the head makes fruitless an investigation of other etiological factors for that anatomical site (L. Hillström and G. Swanbeck, 1970). However, an investigation of 100 cases of the trunk in Sweden indicated 22 were associated with the following: burn scar (3), mechanical trauma (3), psoriasis (3), eczema (3), other skin diseases (3), fistulas (4), and X-ray treatment (3). Of 143 patients with squamous cell carcinoma of the trunk, only 21 patients had a non-ulcerating tumor (G. Swanbeck and L. Hillström, 1969). Of the 122 patients with squamous cell cancer in ulcerations or with ulcerated cancer in the trunk, the following associations were found: burn scar (6), mechanical injury (13), Acrodermatitis chronica atrophicans Herxheimer (7), psoriasis (5), eczema (6), other skin disease (6), osteomyelitis (6), unspecified ulcers (68).

Prolonged industrial and environmental exposures other than solar UV radiation have been found to be associated with skin cancer (E. J. Macdonald, 1975), e.g., occupational exposures to polycyclic aromatic hydrocarbons (E. A. Emmett, 1975). Pitch, tar, or tar products are the suspected carcinogens in tar distilling, coal gas manufacturing, pitch loading, briquette manufacturing from pitch, some soaps, varnishes, insecticides, pesticides, and disinfectants (E. J. Macdonald, 1975). Fractionation and distillation products of oils are also suspected etiological agents in the following occupations: shale oil workers, cotton mule spinners, paraffin wax workers, mineral cutting oil users, and refinery workers.

Arsenic is a skin cancer carcinogen that has been found in the drinking water in certain population groups residing in Poland, Argentina, and Taiwan (S. Yeh, 1973). In a population of approximately 100,000 on the southwest coast of Taiwan, a skin

cancer prevalence rate of 10.6 per 1,000 was found with a male/female ratio of 2.91:1 (S. Yeh, 1973). This population had been drinking artesian well water with a high concentration of arsenic for more than 50 years. A retrospective study of skin cancer in Lane County, Oregon, however, found no correlation between incidence and arsenic levels in the drinking water (W. Morton et al., 1976). The authors state that fewer than expected drinking water sources were found to contain high arsenic content, so that the Lane County data does not necessarily contradict previous reports of positive correlation.

It was found in Southern Texas that the squamous cell carcinomas resulting from non-solar-induced exposures are the ones that are most likely to metastasize (E. J. Macdonald, 1975). Metastasis in sun-induced squamous cell cancer was found to occur in less than 1 percent of such cases. In squamous cell cancer of the head and neck, 496 individuals had 755 metastases in a total of 8,601 cases. Of 30 percent of skin cancer patients with squamous cell cancers, among males 3.6 percent had metastasis by the end of the fifth year, and among females 1.7 percent had metastasis by the end of the fifth year.

Genetic predisposition to squamous and basal cell carcinoma has been shown to exist in studies for population groups residing in Galway, Ireland, New York City, and Philadelphia (S. F. O'Beirn et al., 1968; G. A. Gellin et al., 1966; and F. Urbach et al, 1971). In Philadelphia, it was found that the proportion of Irish and English (including Scottish and Welsh) ancestry was significantly greater in cancer patients than in the control groups, while the proportion for those of Slavic ancestry was smaller (Urbach et al, 1971).

6.2 BASAL CELL CARCINOMA

The evidence associating solar ultraviolet radiation as the most significant factor in the etiology of basal cell carcinoma is almost as convincing as that for squamous cell carcinoma.

One missing piece of evidence is the ability to induce basal cell carcinoma in rodents with ultraviolet radiation. The strong correlation of incidence with exposure of anatomic site is also weaker for basal cell carcinoma. This can be seen in Table 10 (F. Urbach, 1969) for two large series of cases obtained from 1920 to 1935 at the Radiumhemmet and from 1957 to 1962 at the Skin and Cancer Hospital of Philadelphia. For the head and neck, it was found that approximately 38 percent of all basal cell carcinomas arose in areas of the skin receiving less than 20 percent of the maximum of ultraviolet radiation, while squamous cell carcinoma occurred only rarely on these sites.

TABLE 10. COMPARISON OF DISTRIBUTION OF BASAL CELL CARCINOMA AND SQUAMOUS CELL CARCINOMA OVER PROTECTED AND UNPROTECTED AREAS OF THE HEAD AND NECK. EXPERIENCE OF THE SKIN AND CANCER HOSPITAL TUMOR CLINIC, 1957-1962, AND OF THE RADIUMHEMMET

Area	S and C Hospital			Radiumhemmet		
	Male %	Female %	Total %	Male %	Female %	Total %
BASAL CELL CARCINOMA						
Head and neck (unshaded)	63.3	63.0	63.2	57.1	67.3	62.2
Head and neck (shaded)	36.7	37.0	36.8	42.9	32.7	37.8
SQUAMOUS CELL CARCINOMA						
Head and neck (unshaded)	100	88.0	94.0	84.2	90.0	86.5
Head and neck (shaded)	0	12.0	6.0	15.8	10.0	13.5

There is evidence that some community-wide urban environmental variable (e.g., air pollutants) may be significant in the induction of basal cell carcinoma (W. Morton et al., 1976). In Fig. 53 individual census tracts in Lane County, Oregon, characterized by high risk of squamous cell carcinoma in relation to their population age distributions, are divided into

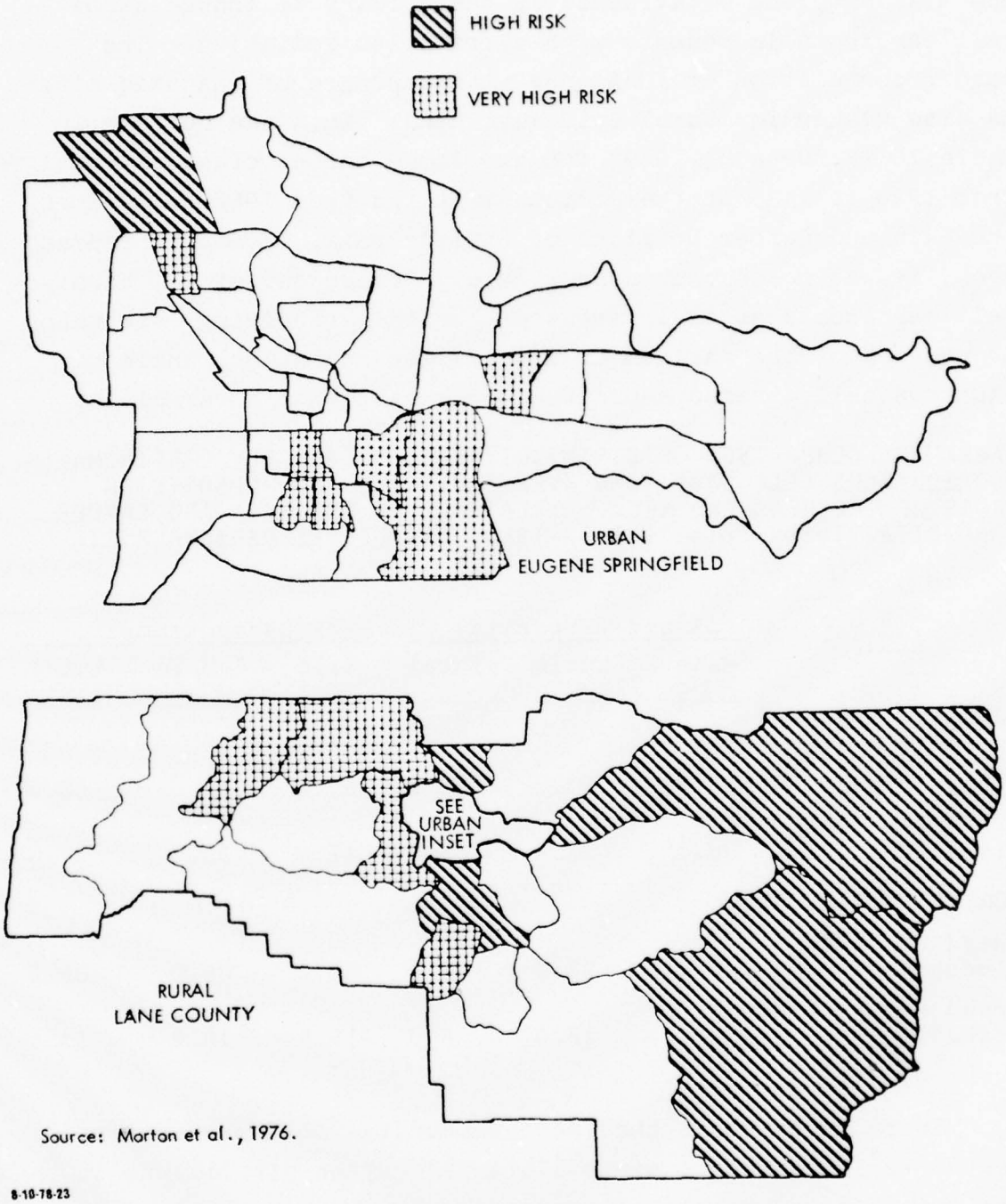


FIGURE 53. High-risk census tracts for squamous cell carcinoma of the skin in Lane County, 1958-1971

risk categories high and very high. A variety of urban and rural census tracts showed a high risk of squamous cell carcinoma. The high-risk census tracts for basal cell carcinoma (Fig. 54) yielded a different geographic pattern in which high risk was concentrated almost entirely within the urbanized core of the county.

Further evidence of the existence of an urban carcinogen in the etiology of basal cell carcinoma is found in the low basal/squamous incidence ratio of 3.32 for the state of Iowa compared to 5.46 and 6.14 for the cities of San Francisco-Oakland and Minneapolis-St. Paul, respectively (F. Urbach and J. Scotto, 1975). A Dallas-Ft. Worth ratio of 3.45 is not surprising since the relative effect of the urban carcinogen could be expected to be reduced in a city of high solar insolation. Indeed, in sun-drenched El Paso there were a total of 30,912 basal cell carcinomas in the period 1944 to 1966 and 13,055 squamous cell carcinomas, yielding a basal/squamous cell carcinoma ratio of 2.37 (E. J. Macdonald, 1975).

If it is assumed that the urban carcinogen is effective in inducing basal cell carcinoma but not squamous cell carcinoma, as indicated by Figs. 53 and 54, then it may be deduced from the above discussion that in northern U.S. cities the risk of basal cell carcinoma is much higher than in rural areas at the same latitude. Indeed, the urban pollutant in northern cities is apparently almost as significant a factor in the etiology of basal cell carcinoma as solar ultraviolet radiation.

Another piece of evidence of the presence of an urban pollutant in basal cell carcinoma is the sharp increase with time of the basal/squamous tumor ratio in Houston, Texas (Fig. 27). During the period over which the increase was observed, 1958 to 1967, and the preceding decade, Houston experienced very high population growth and urbanization.

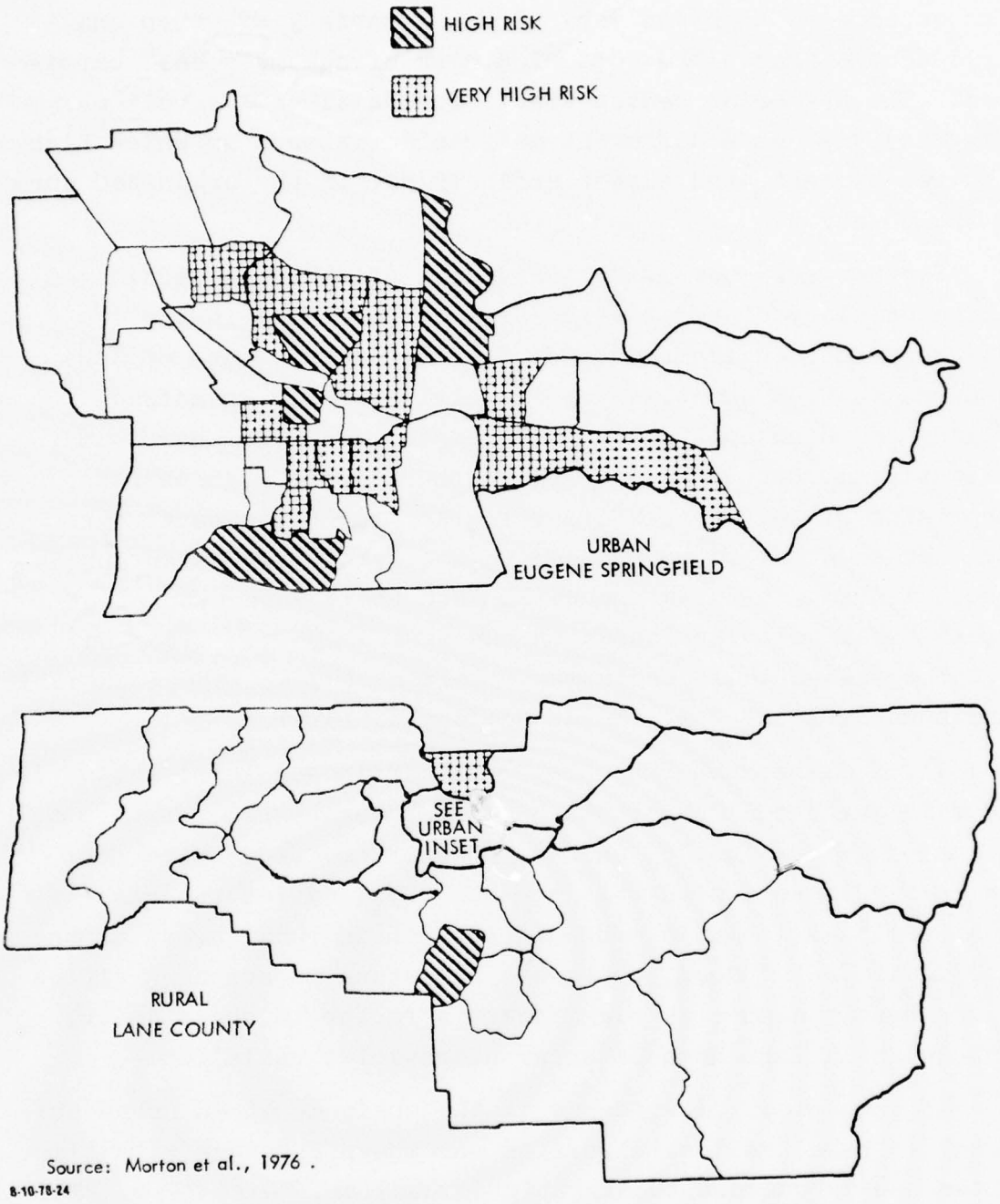


FIGURE 54. High-risk census tracts for basal cell carcinoma of the skin in Lane County, 1958-1971

6.3 MALIGNANT MELANOMA

The evidence for associating solar UV radiation with malignant melanoma, as summarized by the National Academy of Sciences (1976), consists of the following:

1. The latitude dependence "appears well established." However, only U.S. incidence data were considered.

2. Anatomic sites least exposed to solar radiation are very rare, e.g., regions routinely covered by bathing suits. However, as acknowledged, melanomas are not concentrated on the most exposed regions of the body, e.g., head and neck (Figs. 41-43), as is the case for squamous and basal cell carcinomas.

3. Some differences in patterns of location in anatomic site between sexes correspond to differences in exposure to sunlight, e.g., higher incidence for the legs of females (Figs. 41-43). However, the low incidence for the head and neck is essentially the same in both sexes, despite the fact that male outdoor exposure must surely exceed female.

There is some evidence indicating that there may be significant but not very large ethnic differences in the susceptibility of Caucasian populations to malignant melanoma (Figs. 11-13). However, in Queensland a control group study of melanoma patients found no marked differences with hair, eye or skin color, or Celtic ancestry (Beardmore, 1972).

The evidence on degree of outdoor exposure is contradictory. While Fig. 13 indicates an association of malignant melanoma with increased outdoor exposure, there are clinical impressions (G. Olsen* and National Academy of Sciences, 1976) that most cases of malignant melanoma are found among people in the younger middle

*Personal Communication with G. Olsen, Finsen Institute, Copenhagen.

and upper class. In treating some 2,000 patients of malignant melanoma over her long career as a plastic surgeon, Dr. G. Olsen of the Finsen Institute could not recall a single patient who had dirty fingernails.* Reinforcing these clinical impressions are data from England and Wales (J. A. H. Lee, 1975 and R. R. Williams and J. W. Horm, 1977) indicating an excess mortality of malignant melanoma in professional and managerial workers as compared to semiskilled and unskilled workers. The social distribution for mortality from other skin cancer was opposite as would be expected from the number of outdoor workers in the latter group.

Experimenters have not been successful in inducing malignant melanoma in animals by ultraviolet radiation alone. This particular lack of biological evidence does not rule out the possibility that ultraviolet radiation is a significant etiological factor for malignant melanoma in humans, as has been illustrated for the case of basal cell carcinoma.

While some of the anomalies in the association of ultraviolet radiation with malignant melanoma have been recognized by epidemiologists (J. A. H. Lee, 1975), there has been great reluctance in the literature to abandon the hypothesis that the primary etiological factor in the induction of malignant melanoma is solar ultraviolet radiation. The very large number of significant anomalies of various kinds in this hypothesis, which were discussed in Sections 2 to 5 of this report, make it highly unlikely that they will be resolved by the modification of past or the proposal of future postulates based on the differential exposure behavior of population groups, solar circulating factor (J. A. H. Lee, 1972), etc. While some synergistic secondary role for ultraviolet radiation cannot be ruled out, the primary culprit(s) must evidently be sought elsewhere.

Characteristics of the three types of malignant melanoma tumors are reproduced in Table 11 (National Academy of Sciences, 1976). Frequency distributions of these three tumor types at

*Personal communication with Dr. G. Olsen, December, 1977.

TABLE 11. PRIMARY MELANOMA OF SKIN (IN WHITE PERSONS)

Type of Melanoma	Median Age, yr	Specific Sites*	Rate of Development	Appearance
Lentigo-maligna melanoma	70	Face, neck and hands	Slow: 5-20 yr	Predominantly flat spot 2-20 cm in size, with *irregular* borders and with raised portions throughout.
Superficial spreading melanoma	56	Face, neck, upper trunk, and lower legs (in females)	Moderately slow:1-7 yr	The brown or black color is notched; or speckled; blue, white, and red; or both
Nodular	49		Rapid: months	Isolated small (3.0 cm) nodule with *smooth* borders; color uniform blue-black

*All three types occur either on the exposed parts of the face, neck, and hands or on the relatively exposed areas of the chest, back, and legs. Only a few lesions are seen on covered areas such as the breasts of females, bathing trunk areas of males, and bathing suit areas of females.

Source: National Academy of Sciences, 1976

four U.S. hospitals based on analysis of a total of 1073 melanoma cases are reproduced in Table 12 (T. B. Fitzpatrick, 1977). Frequency distributions for only 137 melanoma patients in the Cambridge, England area were in fair agreement with the data of Table 12, showing frequencies of 11 percent for lentigo-maligna, 50 percent for superficial spreading, and 39 percent for nodular melanoma (L. Bakos and A. L. Macmillan, 1972). Note from Table 11 that lentigo-maligna melanoma are more commonly found in the most exposed sites of the face, neck, and hands, and so this type of tumor could be rationally suspected of being related to solar ultraviolet radiation. The slow rate of development (5 to 20 years) of this type of tumor and the fact that it is usually found among the elderly (median age of 70 years) is also consistent with the solar ultraviolet hypothesis. However, note that the frequency of this type of tumor (Table 12) is 5.5 times higher in the hospital in Philadelphia than in the hospital in San Francisco, a more southern U.S. City with a much milder climate. The lower 99 percent confidence limit for the Temple University lentigo maligna melanoma frequency of 7.8 percent, based on a population of 320 cases, is approximately 4 percent (Eisenhart et al., 1947). This value is triple the observed San Francisco Hospital frequency of 1.4 percent. This large frequency difference therefore represents yet another anomaly for the solar ultraviolet hypothesis. However, the data are not inconsistent with a hypothesis in which some unknown carcinogen X is more efficient in the production of lentigo-maligna melanoma in Philadelphia as compared to San Francisco.

The younger median age of 56 years for superficial spreading melanoma, the tendency for the tumor to locate in the trunk and lower legs, the high frequency (63 to 74 percent), and the moderately slow rate of development (1 to 7 years) suggest an

TABLE 12. PERCENTAGE OF TYPE OF MELANOMA BY INSTITUTION*

Institution	No. of Cases	Lentigo-Maligna Melanoma, %	Superficial Spreading Melanoma, %	Nodular Melanoma, %	Indeterminate, %	Unknown, %
Massachusetts General Hospital	228	3.5	70.6	17.9	5.2	2.6
San Francisco Hospital	136	1.4	65.4	17.6	5.8	9.5
New York University Hospital	389	3.8	73.7	13.3	8.7	0.2
Temple University Hospital	320	7.8	62.8	14.3	12.5	2.5
All	1073	4.6	68.7	15.1	8.7	2.6

*Personal communication with T. B. Fitzpatrick, Harvard Medical School, August 1977.

association with unknown carcinogen Y. The still younger median age of 49 years for nodular melanoma and still more rapid development time measured in months suggest an even stronger association of nodular melanoma with carcinogen Y.

In Table 13 are given some plausible characteristics of carcinogens X and Y which might serve to guide future efforts in unravelling the mysteries of the etiology of malignant melanoma. If this two-carcinogen hypothesis is correct, carcinogen Y clearly poses the more severe threat to public health.

TABLE 13. HYPOTHETICAL CHARACTERISTICS OF MALIGNANT MELANOMA CARCINOGENS

Carcinogen	Type of Tumor Induced	Most Effective Geographic Regions	Least Effective Geographic Regions	Favored Anatomical Sites	Time Behavior	Origin in Time
X	Lentigo-maligna melanoma, Superficial spreading melanoma	Australia, New Zealand, Scandinavia, Hawaii	Southern Europe	Head, hand, foot	Invariant	Not applicable
Y	Superficial spreading melanoma, nodular melanoma	↓	↓	Trunk, lower leg	Increasing	~1880

A tentative rationale for the hypothetical carcinogen characteristics of Table 12 can be made, but it is quite likely that revisions, e.g., another carcinogen, will be needed as gaps in the presently available information for the three types of tumors are filled. The 5 percent frequency for lentigo-maligna melanoma is too low to account for the approximately 20 percent frequency registered for the head and neck (Figs. 41 through 43). It is therefore necessary to tap the superficial spreading melanoma

group of tumors which account for approximately 70 percent of malignant melanoma tumors. This tap of approximately 15 percent is large compared to the lentigo-maligna group, but small in comparison to the remaining 55 percent for the superficial spreading melanoma group which affects primarily the trunk and lower leg. The median age for the reduced superficial spreading melanoma group would be lower than the reported 56 years.

There is evidence that urbanization increases the risk of malignant melanoma. In rural Warsaw, Poland, the age-standardized melanoma rate for the period 1968 to 1972 was 1.1 per 100,000 for both sexes; in the city of Warsaw it was 3.2 for males and 2.7 for females (J. Waterhouse, et al., 1976). Incidence rates for rural Norway are lower than for urban Norway (Figs. 7 and 8), but the differences are not as striking as they are for Warsaw. Incidence rates for Finland in 1953 to 1959 and 1961 to 1970 are reproduced in Table 14 by geographic area, sex, and residence (L. Teppo, et al.). Geographic areas I to IV are shown in Fig. 55. Note that nearly all of the urban rates exceed the rural rates in a given geographic area, and the total rates for the more urbanized areas III and IV are greater than the values for areas I and II. Finally, malignant melanoma incidence is lower in rural Denmark than in the capital city of Cophenhagen (J. Clemmesen, 1977).

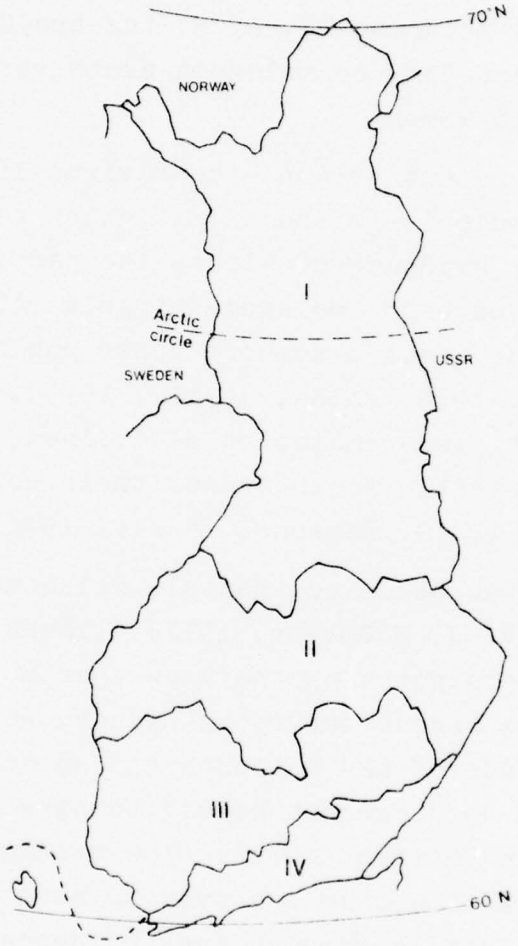
Trauma has long been suspected of being a cause of malignant melanoma, but some dermatoligists consider this a myth (R. Jackson, 1971). There has never been a single documented case report of trauma of any sort changing a histologically benign naevus into a histologically proven malignant melanoma (Walton and Cox, 1963). On the other hand, a retrospective method comparing the incidence of traumas in malignant melanoma with the incidence of traumas in a control series of basal cell carcinomas indicated that trauma was a factor in the production of malignant melanoma (A. J. Lea,

1965). Although certain tribes of India who do not wear shoes have a higher incidence of malignant melanoma on the plantar surfaces (Sirsat, 1952), the incidence of malignant melanoma in South African Negroes in the Johannesburg area has not decreased with urbanization and shoe wearing (Davis, 1959). The incidence of melanoma in the foot of pigmented races was much higher than amongst whites (V. J. McGovern, 1977). The ultraviolet hypothesis is obviously incompatible with these findings.

TABLE 14. MEAN ANNUAL AGE-ADJUSTED INCIDENCE RATES (PER 10^5) OF CUTANEOUS MELANOMA IN FINLAND IN 1953-1959 and 1961-1970, BY GEOGRAPHIC AREA (I-IV, SEE FIG. 55), SEX AND RESIDENCE.

Sex and Residence	1953-1959				1961-1970			
	I	II	III	IV	I	II	III	IV
Males								
Urban	1.33	1.74	1.99	1.85	3.67	3.12	2.93	3.55
Rural	1.16	1.22	2.22	2.10	1.77	2.12	2.25	2.10
Total	1.21	1.32	2.15	1.96	2.29	2.38	2.51	3.03
Females								
Urban	3.24	2.05	2.14	2.67	1.63	3.12	2.86	3.11
Rural	1.23	1.20	1.58	2.00	2.21	2.12	2.09	1.87
Total	1.63	1.42	1.81	2.43	2.05	2.32	2.47	2.72

There is evidence of a genetic factor in malignant melanoma. A study of 113 family histories from a total of 125 consecutive cases of malignant melanoma in Brisbane, Australia, covering 923 first-degree relatives, showed a heritability of liability of approximately 11 percent (D. C. Wallace et al., 1971). Other surveys have shown 1 to 7 percent of the total patients have given information of relatives with malignant melanoma (C. M. Sutherland et al., 1976). Since relatives might be exposed to the same kinds of carcinogenic agents, it is difficult to judge the significance of these findings.



Source: L. Teppo et al.

FIGURE 55. The four areas (I-IV) used in the analysis of the geographic variation in the risk of cutaneous melanoma in Finland

The role of pregnancy in producing malignant melanoma in women has been investigated. It was concluded that any production of malignant melanomas by the stimulation of melanocytes in pregnancy must form a very small proportion of the total incidence of malignant melanoma (J. A. H. Lee and G. B. Hill, 1970). There was no difference in the melanoma death rate between married and unmarried women.

There has been recent evidence that virus-like particles are present in the majority of human malignant melanomas. In Brisbane, Australia, evidence of virus-like particles was found in 15 out of 26 (58 percent) melanoma biopsies (P. G. Parsons, et al., 1976). These results support other published evidence (Brickmayer, et al., 1974; Balda, et al., 1975). The exact nature of these particles remains to be defined, and until this is done it is not possible to interpret their role in the induction of melanoma (P. G. Parsons, et al., 1976).

Until 1892 it was believed that all melanomas arose in preexistent moles (V. J. McGovern, 1977). There is today circumstantial evidence supporting the view that most melanomas arise in naevi. One recent survey in Sydney, Australia found that nearly two-thirds of 824 patients had an antecedent skin blemish, while only 29.3 percent seemed to have arisen de novo in blemish-free skin (Milton, 1972). The average student at Sydney University was found in a survey to have 16 moles (V. J. McGovern, 1977). If it is assumed that 60 percent of melanomas arise from a preexistent mole, and the incidence of malignant melanoma is 16 per 100,000 in Queensland, and the number of moles does not increase with age, then the probability of a mole becoming malignant is 6×10^{-6} per year, and correspondingly less in regions of smaller incidence. Of course, the number of moles on a person does increase with age and the true probability is therefore smaller and varies with age.

At present, there is a controversy over whether or not diet is an important factor in the etiology of malignant melanoma. In over 500 consecutive patients who came to a plastic surgeon's office in Los Angeles, 54 percent forced polyunsaturated foods into their diet, and 60 percent of this group had had at least one skin lesion removed because of suspected malignancy after their having altered their dietary fat, while only eight percent of those who made no special effort to eat polyunsaturates reported removal of any precancerous or cancerous lesions from their skin at any time in the past (E. R. Pickney, 1973). In Sydney, Australia, five cases of malignant melanoma of the lower limb (four in females) were treated in a 12-week period in a private dermatological practice (B. S. Mackie, 1974). It was found that all five patients had changed from butter to polyunsaturated margarine as a spread and all had changed to polyunsaturated oil or margarine for cooking some time before the lesion was observed. A random survey of 100 patients indicated that 34 patients had used polyunsaturates for six months or more, 12 had used some polyunsaturates and 54 had used little or no polyunsaturates. Mackie states that it is a common observation that cutaneous reactions to oral chemicals tend to affect the legs first. His explanation is that probably the sluggish circulation of the legs allows longer periods of cellular exposure to the chemicals and permits a buildup of larger molecules. Therefore, he reasons, if a dietary factor can accelerate the onset of malignant melanoma, it would be quite likely to affect the legs first. If there is a difference in the circulation patterns for the left and right leg, some additional support to Mackie's explanation may be found in the anomalous asymmetry in the distribution of the number of female cases arising between the ankle and knee (National Academy of Sciences, 1976). In a photograph exhibiting the localization of melanoma skin cancer in 534 males and females, 35 melanomas can be counted for the left female leg but only 15 for the right female leg.

There followed a control group study (R. B. Goldricks, et al., 1976) of 29 patients with malignant melanoma and 31 patients with benign naevi. It was found that patients with malignant melanoma had not consumed excessive quantities of polyunsaturated fats, and that therefore there was no evidence to indicate that ingestion of polyunsaturated fats is associated with an increase in incidence of melanoma. This study was criticized (J. W. Donovan, 1976) on the grounds that the controls were suffering from a related condition, i.e., if both benign naevi and malignant melanomas were caused by polyunsaturates, the study as designed would falsely have failed to show any association. The reliability of the questionnaire was also criticized, leading to the conclusion that Mackie's suggestion had not been given a fair test.

There has been observed a spontaneous regression in primary as well as secondary tumors, a phenomenon that seems probably related to immunological factors (V. J. McGovern, 1977) and has only been recognized in cutaneous tumors. About 7 to 8 percent of all melanoma metastases have no demonstrable primary.

From the above discussion it is apparent that the etiology of malignant melanoma is today in a chaotic state. However, there are hints that important etiological breakthroughs may be made in the near future, particularly in virology and dietetic factors.

7. MODELLING OTHER SKIN CANCER INCIDENCE

7.1. CHANGE IN ULTRAVIOLET RADIATION DOSE

The problem of predicting the percentage change in erythemally weighted ultraviolet radiation incident on the surface of the earth for a specified percentage change in the thickness of the stratospheric ozone layer has been calculated by a number of investigators (Latarget, 1935; Schultze, 1974, Cutchis, 1974; Green et al., 1974). This is a purely physical problem, and if all investigators used the same erythemal response curve, they should have arrived at essentially the same answer. It is therefore not surprising that they agree that a postulated 1 percent decrease in the thickness of the stratospheric ozone layer would result in approximately a 2 percent increase in the ultraviolet radiation dose at mid-latitudes. The ratio of percentage change in UV dose to percentage change in ozone thickness is commonly referred to as the amplification factor A_u. For small changes in ozone (less than 20 percent) A_u remains essentially constant at the value of two, but increases with higher values of ozone depletion and with increasing latitude. At a latitude of 60^o, a 50 percent ozone depletion would result in a 200 percent increase in UV dose, i.e., $A_u = 4$ (Schulze, 1974). Most calculations for the amplification factor are based on clear sky conditions. Recent ground measurements indicate that because of the presence of clouds A_u may have a slightly smaller value than 2.0 (L. Machta et al., 1975).

7.2. CHANGE IN OTHER SKIN CANCER INCIDENCE

The most difficult and controversial part of predicting the change in skin cancer incidence for a specified change in ozone

thickness is the problem of determining the change in incidence for a specified change in UV dose, or the amplification factor A_s. The overall amplification factor A relating change in skin cancer incidence to change in ozone thickness is given simply by

$$A = A_u A_s \quad . \tag{1}$$

The first calculation of the amplification factor A was made by J. E. McDonald, who arrived at a value of six on the basis of the latitudinal gradient of the skin cancer incidence observed in many areas of the world among ethnically homogeneous populations (J. E. McDonald, 1971).

Urbach and Davies (1975) developed a model in which the following assumptions were made:

1. Biologically-active UV dose is a linear function of latitude, within the limits of immediate interest, i.e., the latitude band between Dallas, Texas and Minneapolis, Minnesota.

2. There exists a latitude dependent "effectiveness factor" which relates the biologically active UV dose to the biologically effective dose actually reaching the target population and which is assumed to be a linear function of latitude.

3. The incidence of skin cancer is a function of the "effective dose" of biologically active UV, that portion of the input dose which actually reaches the target population. In the absence of adequate data for man, the relationship is assumed to be linear.

The results showed about a 10 to 15 percent increase in incidence, depending on U.S. city and sex, for a 10 percent increase in biologically effective ultraviolet radiation. Lower percentage increase values were predicted for the lower latitudes in the U.S. and these values for males were higher than for females.

These percentage increases were almost doubled for Dallas and tripled for Minneapolis when calculations were based on total instead of effective UV dose.

A. E. S. Green and T. Mo (1974) suggested an exponential model of age-adjusted incidence rate R. In such a model

$$R = R_o \, e^{\alpha D} \quad , \tag{2}$$

where D is UV dose, α is a constant, and R_o is the incidence rate at zero dose. Such a model has also been used by the National Academy of Sciences (Scott et al., 1975). This model suffers from the fact that R_o should be equal to zero and obviously cannot be if Eq. (2) is to be meaningful. The value of R_o used by Green (1976) is 11.1 per 100,000. If this value is interpreted to represent non-UV related skin cancer incidence, then it is far too low a value. As discussed in Section 6.2, the incidence of basal cell carcinoma in northern U.S. cities for cases not related to solar ultraviolet radiation may be as large as the UV-related incidence. Exponential models lead to high amplification factors for large percentage increases in UV dose, e.g., a 20 percent increase in UV dose has been calculated to result in a 71 percent increase in male non-melanoma incidence for Oklahoma (Fears et al., 1976).

Green et al. (1976) present a mathematical argument that indicates the gross nature of the dose dependence of age-adjusted skin cancer incidence should exhibit a power law behavior, i.e.,

$$R = K \, D^n \quad , \tag{3}$$

where K and n are constants. This power law has several attractive features. The incidence rate approaches zero as the UV dose

D approaches zero, and the constant n is the amplification factor since

$$\frac{dR/R}{dD/D} = n \quad . \tag{4}$$

Green et al. (1976) found that the best fit to their worldwide data was a power law with K = 177 and n = 1.77 $\pm$ 0.24. They also found that the biological amplification factor of 1.8 for the U.S. population center was greater in regions of higher UV annual dose, and smaller in regions of lower annual UV dose.

A "dynamic" model of skin cancer incidence has been used by P. C. Beadle* in which population sensitivity and exposure are treated as variables. Sensitivity-exposure categories are defined which form a smoothly increasing sensitivity-exposure distribution. This model predicted a 37 percent decrease for a 10 percent decrease in UV dose and a 51 percent increase for a 10 percent increase in UV dose. It also predicted a rapid initial increase in incidence following a sudden step function increase in UV dose which differs from the gradual temporal response predicted by Cutchis (1975). A sudden (within the first year) increase of 20 percent of the saturation value expected a century later, when the population is in equilibrium with the new UV environment, is predicted by Beadle's computer calculations. It is a result which is surprising and difficult to explain since 1 year of exposure to even a 50 percent increase in UV dose constitutes but a small fraction (approximately 1 percent) of the accumulated lifetime dose of the elderly population in which most skin cancers occur.

R. D. Rundel and D. S. Nachtwey have developed a model (D. Kennedy, 1977) which uses the age-specific incidence curve to derive a dose-response model for a given region. It has the

*Private communication, Environmental Sciences Group, British Aircraft Corporation.

advantage of avoiding the difficulties inherent in comparing different regions with different ethnic population groups, climates, life styles, etc. However, it relies on age-specific curves in the U.S. which are unreliable because of migration and because the data used is based on the NCI survey (see Appendix A). Another objection to this model is the trade-off assumed between age and UV dose, e.g., the 35 to 45 year age group, if subjected to the lifetime dose of the 45 to 55 year age group, is assumed to have the incidence of the latter. The shape of the age-specific curves for the young age groups belies this assumption. The age group 15 to 25 years is almost immune to skin cancer, and to predict that the incidence of that age group, if subjected to the lifetime dose of 25 to 35 year group, would have the same incidence as the latter would certainly represent a gross overestimate. The problem here is that chronological age is a concrete and fundamental biological parameter which should not be confused with a nebulous UV age parameter. This model, which assumed a log-normal dose response relationship, predicted that for the U.S. as a whole, a 1 percent decrease in stratospheric ozone thickness, corresponding to a 2 percent increase in UV dose, would lead ultimately to an increase of 8 percent in skin cancer incidence, i.e., a biological amplification facter of 4.

7.3 THE SOLAR RADIATION EXPOSURE FACTOR

Probably the most significant and difficult factor to quantify in any model of the dose-response relationship is the sun exposure factor for different population groups. A power law model will be used below to demonstrate how these exposure values are related to the amplification factor. The annual UV dose D is assumed to be the product of the exposure E of that group and the annual ultraviolet radiation reaching the ground U at a given geographic site. Thus, from Eq. (3),

$$R = K E^n U^n \quad . \qquad (5)$$

The exposure factor E may be interpreted as the fraction of the annual UV dose received by a target population and depends on climatic and life-style factors. The absolute value of E will be unimportant to the model as used below, but the ratio of the E values for different geographic regions will be seen to be of great importance in determining the most likely value for the biological amplification factor.

Incidence rates for other skin cancer for males and females in Finland, the Canadian provinces of British Columbia and Manitoba, England, and El Paso, Texas will be compared to determine implications with respect to relative exposure between these population groups for different assumed values of the amplification factor. In order to achieve this goal, it is first necessary to assign values to the annual UV dose U for each geographic site.

In Fig. 56 the annual erythemal dose is plotted as a function of latitude for the Northern Hemisphere. The curve was obtained by summing the monthly values calculated by Schulze (1974). The absolute values for U per se are not important to this model but the relative values given by the shape of the curve are. Clear weather was assumed and an ozone layer the thickness of which varied with latitude and season after Dopplick, 1972.

The shape of the curve in Fig. 56 reveals the pitfall some investigators fall into when they cite without qualification a doubling in incidence for every x degrees of latitude change. Clearly, a change of x degrees of latitude at a latitude of 30 degrees involves a much greater absolute or percentage change in UV dose than at the equator or at a latitude of 60° N. Latitude is a poor dummy variable for expressing changes in skin cancer incidence.

Finland at approximately 60° N latitude is chosen as the northernmost geographic site because the data there is relatively

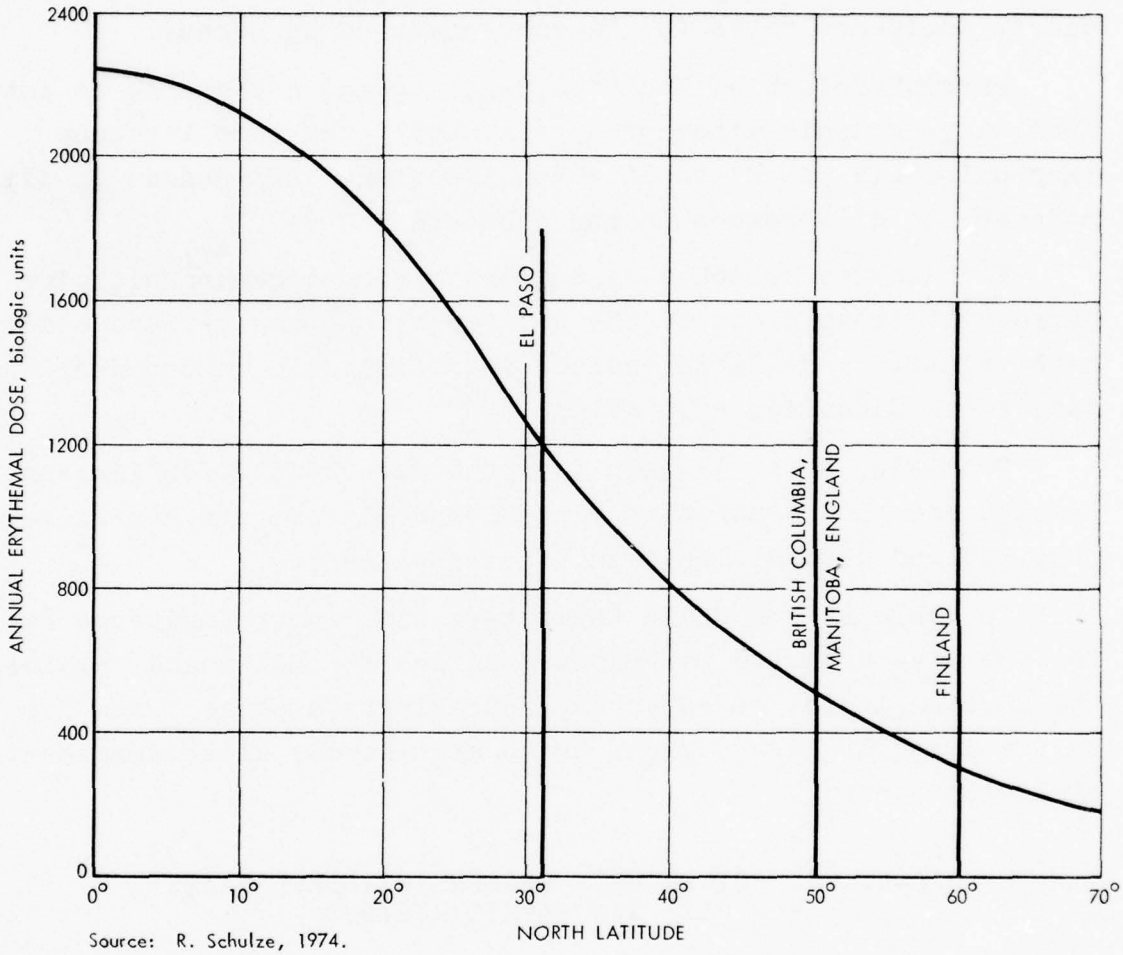


FIGURE 56. Annual erythemal dose for Northern Hemisphere, assuming clear weather conditions

good (compulsory reporting since 1961) and because Finns are of mixed Caucasian origin (only 6.5 percent of the population speak Swedish as their mother tongue) involving Baltic and probably eastern elements (E. A. Saxen, 1976). This ethnic composition is reflected in the approximately 30 percent lower other skin cancer incidence rates for Finland compared to Norway.

British Columbia, Manitoba, and England are chosen as intermediate geographic sites of approximately the same latitude (approximately 50° N) to show how important differences in climate are to differences in sun exposure.

El Paso was selected as the southernmost geographic site because it is as close to the equator as one can get and still have relatively reliable (cancer registry) skin cancer incidence data for a Caucasian population.

From Fig. 56 it is seen that the values of U for Finland, England and the Canadian provinces, and El Paso are approximately 300, 500, and 1200 biologic units, respectively.

In Table 15 are given the other skin cancer incidence rates for the five selected geographic regions for males and females. The England incidence rates are approximate average rates for half a dozen English regions which are in very close agreement with each other.

TABLE 15. OTHER SKIN CANCER INCIDENCE RATES FOR FIVE GEOGRAPHIC REGIONS

GEOGRAPHIC REGION	MALE	FEMALE
Finland	38	34
England	44	25
Manitoba	80	57
British Columbia	149	97
El Paso	202	102

Substituting the incidence rates for Finland in Eq. (5),

$$38 = K(300\ E_{Fm})^n \tag{6}$$

$$34 = K(300\ E_{Ff})^n \quad , \tag{7}$$

where E_{Fm} and E_{Ff} are the exposure for males and females in Finland, respectively.

Dividing Eq. (6) by Eq. (7),

$$\left(\frac{E_{Fm}}{E_{Ff}}\right)^n = 1.118 \quad . \tag{8}$$

Assuming n = 1, and measuring all population exposures relative to that of females in Finland, i.e.,

$$E_{Ff} = 1 \quad , \tag{9}$$

it follows that

$$E_{Fm} = 1.118 \quad . \tag{10}$$

Dividing the equations for incidence rates of males in El Paso and Finland,

$$\frac{202}{38} = \left(\frac{1200}{300}\right)^n \left(\frac{E_{Pm}}{E_{Fm}}\right) \tag{11}$$

or

$$\frac{E_{Pm}}{E_{Fm}} = \frac{5.316}{4^n} \quad , \tag{12}$$

and for n = 1,

$$E_{Pm} = 1.329 \times 1.118$$

$$= 1.49 \quad . \tag{13}$$

Dividing the equations for incidence rates of females in El Paso and Finland,

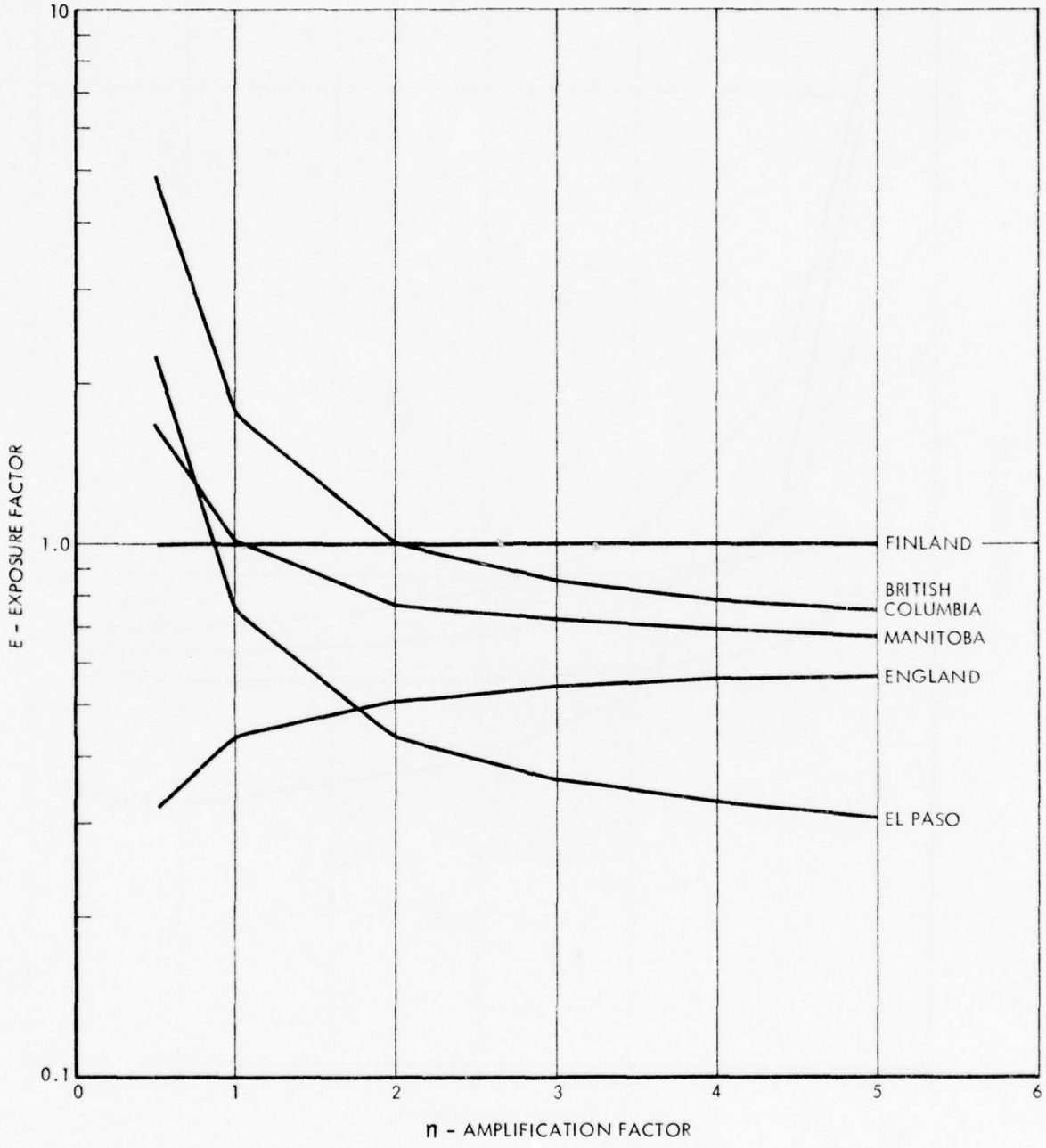
$$\frac{E_{Pf}}{E_{Ff}} = \frac{3}{4^n} \qquad (14)$$

and, for n = 1,

$$E_{Pf} = 0.75 \quad . \qquad (15)$$

From the above data alone, it can be deduced that a biological amplification factor of unity is eminently reasonable. Females in El Paso could be reasonably expected to avoid the hot summer sun in their air-conditioned homes or offices and expose themselves to a smaller fraction of the annual solar ultraviolet radiation incident in El Paso than the fraction in Finland that sun-appreciating females would seek out during their comfortable summers. Many males in El Paso, on the other hand, are constrained by their outdoor occupations and the male group ends up with double the exposure of the female group in this aggregate model.

Exposure factors calculated for other geographic regions and other assumed amplification factors ranging from 0.5 to 5.0 are graphed in Fig. 57 for females and in Fig. 58 for males. The high order of magnitude spread in exposure factors for n = 0.5 (square root dose-response relationship) makes that choice of amplification factor extremely unlikely. The spread in exposure factors is a minimum for n = 2, which appears to make this choice of amplification factor also reasonable. However, the male exposure factor for males in El Paso (Fig. 58) drops in rank from second for n = 1 to fifth for n = 2, and its low value of 0.6 implies a seemingly unreasonable degree of sun avoidance. In any case, an examination of the behavior of the sets of exposure factors in Figs. 57 and 58 leads to a choice of a most reasonable amplification factor in the interval



NOTE: EXPOSURE FACTOR NORMALIZED TO UNITY FOR FINLAND FEMALES

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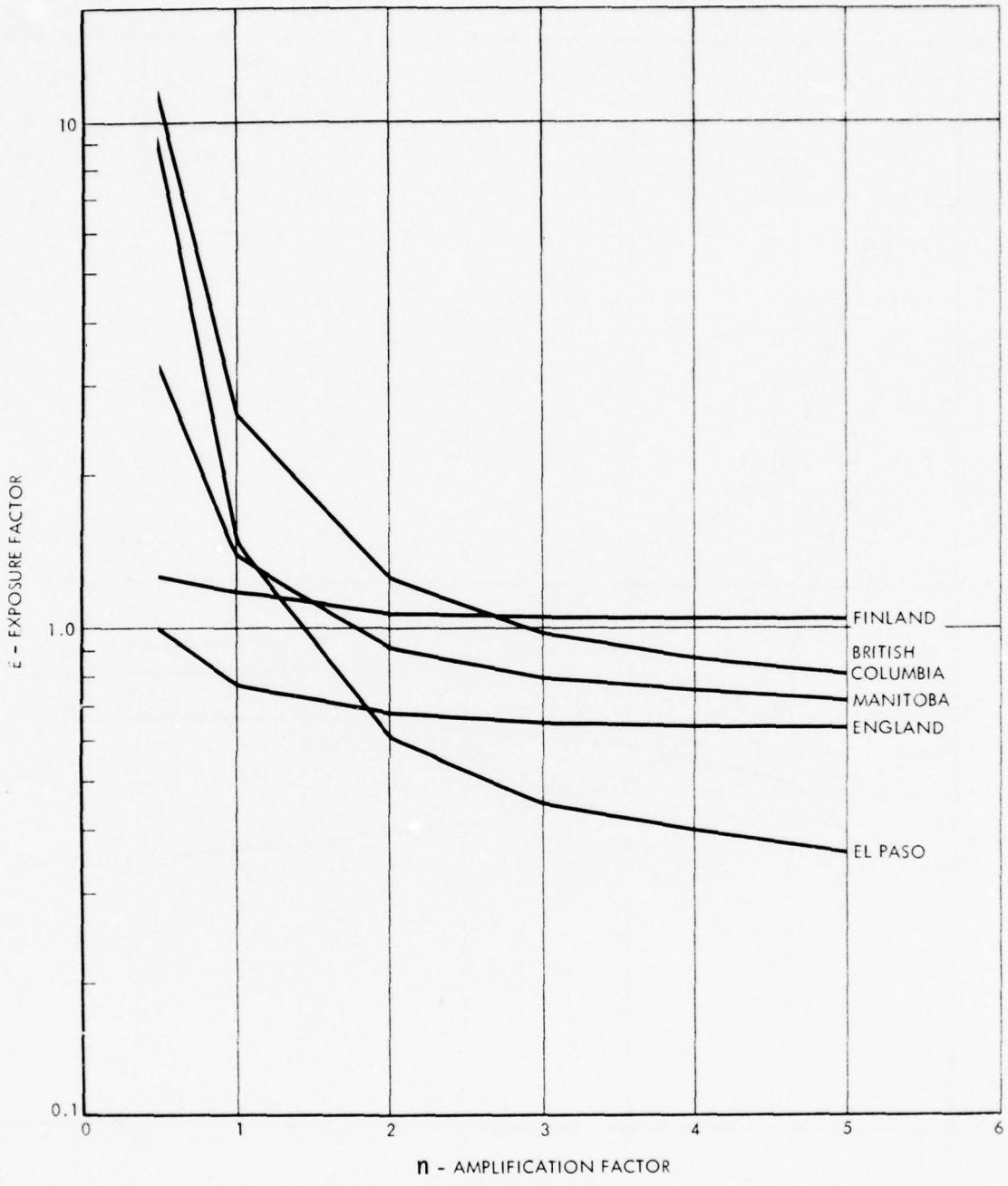
FIGURE 57. Exposure factors for females versus amplification factor



NOTE: EXPOSURE FACTOR NORMALIZED TO UNITY FOR FINLAND FEMALES

FIGURE 58. Exposure factors for males versus amplification factor

$$1 < n < 1.8 \quad . \qquad (16)$$

The value of 1.8 corresponds to the points where the exposure factors for El Paso and England intersect, and agrees with the estimate of Green et al. (1976). The lower values in the interval agree with Urbach and Davies (1975).

In the region given by inequality (Eq. 16) British Columbia has the highest exposure factor of the five geographic regions, lying somewhere between two and three times the exposure factor of England, which lies at approximately the same latitude. This large discrepancy certainly cannot be explained on the basis of an ethnic difference in population. The explanation must lie mainly in the difference in climatic factors and occupations.

The power law model used here allows a ranking of the male/female exposure factor for the five geographic regions. The ranking is independent of the assumed amplification factor, as shown in Table 16. Amplification factors above 2 yield little variation in exposure factor between geographic regions, and all approach unity with increasing n. Since males are known to expose themselves appreciably more to solar radiation than females at lower latitudes, Table 16 also indicates the improbability that the biological amplification factor exceeds 2.

TABLE 16. MALE/FEMALE EXPOSURE FACTOR RATIOS

		n				
	Rank	0.5	1	2	3	4	5
El Paso	1	3.92	1.98	1.41	1.26	1.19	1.15
England	2	3.10	1.76	1.33	1.21	1.15	1.12
British Columbia	3	2.36	1.54	1.24	1.15	1.11	1.09
Manitoba	4	1.97	1.40	1.12	1.12	1.09	1.07
Finland	5	1.25	1.12	1.06	1.04	1.03	1.02

7.4 CLIMATIC FACTORS

One of the most significant climatic factors affecting the solar ultraviolet radiation reaching a target population is cloud cover. Clouds greatly reduce the amount of radiation reaching the ground and discourage recreational activity. In Table 17, the percentage of occurrence of three categories of cloud amount are given for Fort Worth, Texas and Minneapolis, Minnesota during the year 1974, as calculated by R. Penndorf. Minneapolis apparently receives a smaller fraction of its incident solar radiation than Fort Worth.

TABLE 17. COMPARISON OF CLOUDINESS IN FORT WORTH AND MINNEAPOLIS

Cloud Amount	Percentage of Occurrences	
	Fort Worth	Minneapolis
0.0 - 0.1	38	30
0.2 - 0.8	16	10
0.9 - 1.0	46	60

That this is indeed the case can be seen in the monthly frequency statistics for fair weather in Table 18, after R. Penndorf. The cloudless category is defined as less than 0.1 sky cover and the scattered by 0.1 to 0.5 sky cover. As defined, Forth Worth had 16 days more of fair weather than Minneapolis during 1974 and 6 days more between April and September, the period of maximum solar radiation. However, if one compares warm fair days, i.e., fair days during which the temperature rose to above 75° F, Fort Worth had 71 more such days during the year and 39 more between April and September. This comparison is further complicated by the large number of warm fair days during which the temperature exceeds 90° F in Fort Worth. Such uncomfortably hot days tend to drive people indoors for relief, particularly during the noontime hours when the temperature and ultraviolet

TABLE 18. MONTHLY FREQUENCY STATISTICS*
OF "FAIR" DAYS FOR FORT WORTH, TEXAS
AND MINNEAPOLIS, MINNESOTA IN 1974

Fort Worth

Month:	J	F	M	A	M	J	J	A	S	O	N	D	YR	A-S
cloudless	5	9	1	8	1	5	4	-	3	7	7	6	56	21
scattered	4	7	7	4	11	12	22	11	7	8	5	7	105	67
cirrus	3	3	8	5	4	6	-	1	2	1	5	6	44	18
total	12	19	16	17	16	23	26	12	12	16	17	19	205	106
Maximum temperature above 75°F														
cloudless	-	1	1	4	1	5	4	-	3	7	2	-	28	18
scattered	-	2	4	3	11	12	22	11	7	8	3	-	83	66
cirrus	-	-	6	3	4	6	-	1	2	1	-	-	23	16
total	-	3	11	10	16	23	26	12	12	16	5	-	134	100

Minneapolis

all Days														
cloudless	4	7	-	5	-	4	-	-	4	5	2	5	36	13
scattered	7	3	6	6	6	7	20	18	8	7	6	2	96	65
cirrus	7	4	6	7	3	7	2	-	3	7	4	7	57	22
Total	18	14	12	18	9	18	22	18	15	19	12	14	189	100
Maximum temperature above 75°F														
cloudless	-	-	-	1	-	4	-	-	1	-	-	-	6	6
scattered	-	-	-	1	-	4	20	18	2	-	-	-	45	45
cirrus	-	-	-	1	1	6	2	-	-	2	-	-	12	10
Total	-	-	-	3	1	14	22	18	3	2	-	-	63	61

In the above Table YR means total number of days for the year 1974 and A-S means total number of days between April and September.

*By. R. Penndorf, Wellesley Hills, Massachusetts

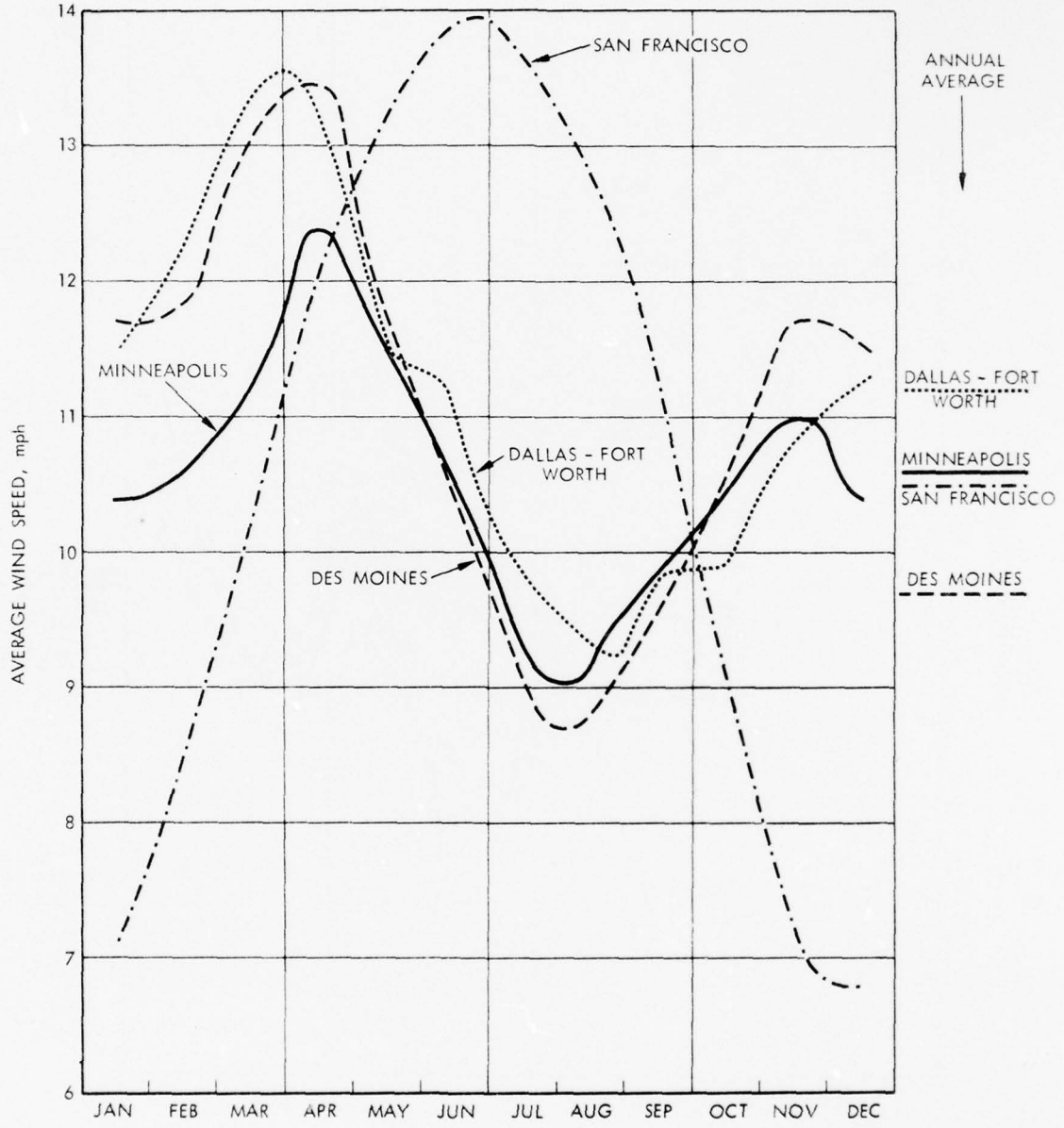
radiation dose are at their maximum values. The percentage of solar ultraviolet radiation that reaches a target population is therefore very difficult to assess in any quantitative way.

Temperature may be a significant biological as well as sociological parameter for the induction of human skin cancer. Mice (40 animals/group) irradiated with sub-erythemal ultraviolet light for 400 days at 90° F were found to develop a significantly larger number of tumors than a control group maintained at room temperature (D. W. Owens, 1977).

Wind may be another climatic variable that may have biologic significance. Mice (30 animals/group), were exposed to ultraviolet radiation daily for 4 weeks with one group protected from the wind and the other exposed to wind of 7 MPH (P. W. Owens, 1977). A significantly greater number of animals exposed to UV radiation and wind developed tumors than those animals receiving UV radiation alone. In Fig. 59 the average-monthly wind speed is shown for four U.S. cities. Note that during the summer months the average wind speed is far higher in San Francisco than in the other three cities.

Finally, relative humidity may also be a biologically significant parameter. Mice (30 animals per group) received sub-erythemal ultraviolet radiation daily with one group of animals maintained at 20 percent relative humidity and the other group at 80 percent relative humidity (D. W. Owens, 1977). Those animals maintained at higher relative humidity developed tumors more rapidly than those maintained at low relative humidity. In Fig. 60 it is seen that San Francisco has appreciably higher relative humidity than the other three cities located in the central U.S. The abnormally high other skin cancer incidence reported for British Columbia may be partly due to the high relative humidity in that Canadian province.

Other climatic factors affecting the UV dose are the natural fluctuations in ozone thickness, smog, ground reflectivity, and altitude.



Source: Statistical Abstract of the United States, 1976.

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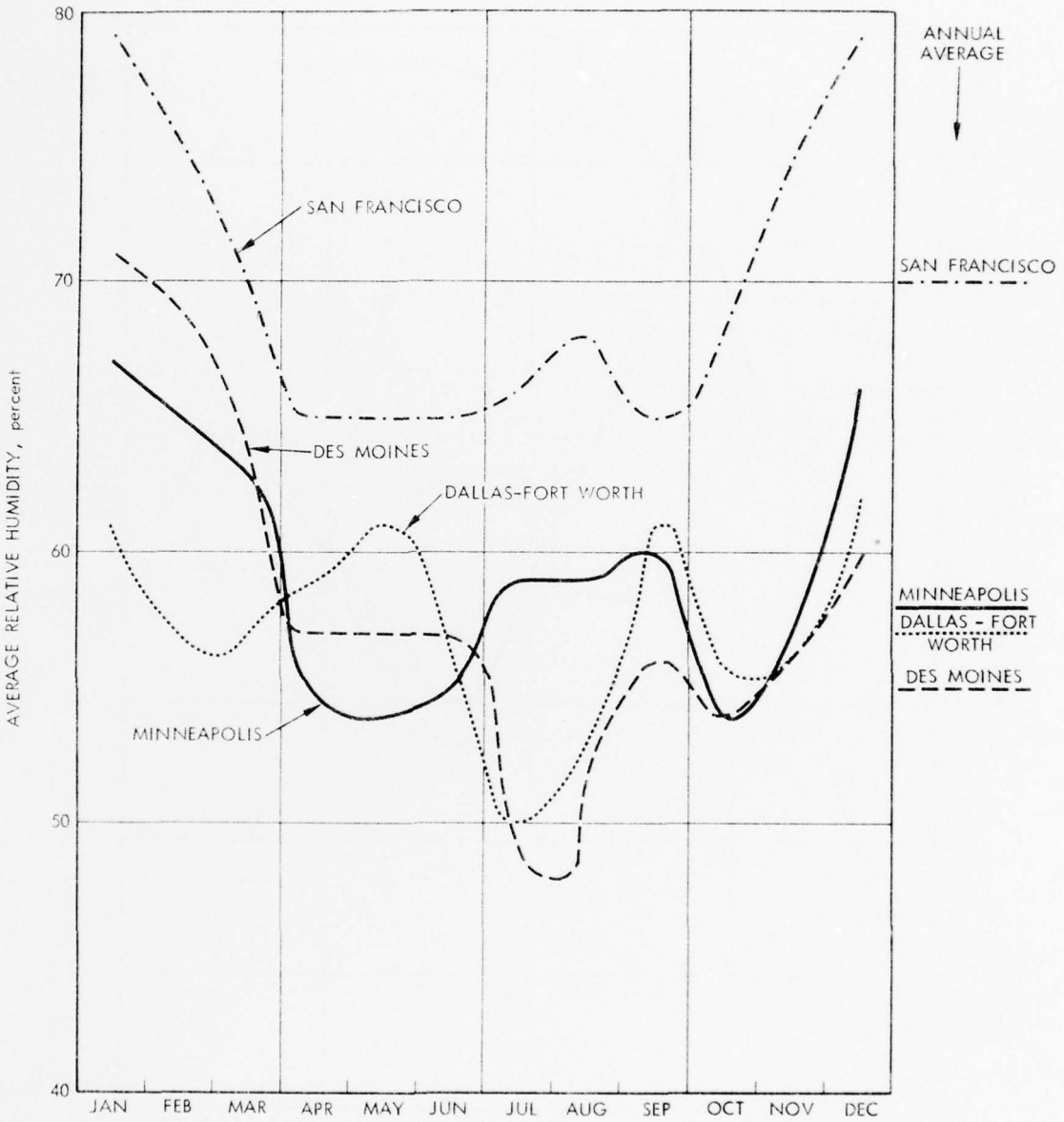
FIGURE 59. Average wind speed for four U.S. cities



Source: Statistical Abstract of the United States, 1976.

FIGURE 60. Average relative humidity at 1:00 pm for four U.S. cities

Other causes for uncertainty in any model of other skin cancer incidence are the appropriateness of using the erythemal response function for skin cancer, the validity of the assumed dose time reciprocity relation, fractionation of dose, the effect of UV immunological factors demonstrated in mice (M. L. Kripke, 1977), artificial sources of UV radiation from sources such as fluorescent lights in offices,* the difference in the UV response of basal and squamous cell carcinoma, the accuracy of the incidence rate data, the wrongful inclusion of non-solar-related carcinomas in the incidence rate data, population migration, ethnic composition, occupations, recreational activities, clothing habits, synergistic effects (e.g., chemicals), etc.

The nature of this complex multi-dimensional problem makes the development of a dose-response model free of uncertainty and controversy an almost hopeless proposition at this time. Ameliorating this doleful conclusion is the knowledge that the biological amplification factor most probably lies between 1 and 2.

To narrow the uncertainty in the determination of the biological amplification factor, perhaps the greatest single step that can be taken is the development of a personal integrating UV dosimeter that can be used to estimate the UV dose received by various populations.

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*Letter from P. Cutchis to A. Broderick, August 12, 1977. Copy available on request.

BIBLIOGRAPHY

Bakos, L. and A. L. Macmillan, "Malignant Melanoma in East Anglia, England," An 11-Year Survey by Site and Type, *British Journal of Dermatology, 88*, 551, 1973.

Balda, B. R. *et al.*, "Oncornavirus-Like Particles in Human Skin Cancers," *Proc. Nat. Acad. Sci. (Wash.), 72*, 3697-3700, 1975.

Barclay, T. H. C., *Cancer Incidence in Saskatchewan, 1969-1972*, In: Waterhouse, J., C. Muir, P. Correa, and Jean Powell, eds., *Cancer Incidence in Five Continents, Volume III*, Lyon, (IARC Scientific Publications No. 15) 1976.

Batten, G. H., *Cancer Incidence in Hawaii, 1968-1972*, In: Waterhouse, J., C. Muir, P. Correa, and Jean Powell, eds., *Cancer Incidence in Five Continents, Volume III*, Lyon, (IARC Scientific Publications No. 15) 1976.

Beardmore, G. L., "The Epidemiology of Malignant Melanoma, in *Melanoma and Skin Cancer*, Proceedings of the International Cancer Conference, *39*, N.S.W. Government Printer, Sydney, 1972.

Birkmayer, G. L., B. R. Balda, F. Miller, "Oncornaviral Information in Human Melanoma," *Europ. J. Cancer, 10*, 419-424, 1974.

Brown, M. M. L., *et al.*, "Genetic Predisposition to Melanoma and Other Skin Cancers in Australians," *The Medical Journal of Australia*, April 17, 1971.

Carmichael, G. G., and H. Silverstone, "The Epidemiology of Skin Cancer in Queensland: The Incidence," *Br. J. of Cancer*, Vol. *15*, 1961.

Christine, Barbara *et al.*, "Cancer in Connecticut, 1966-1968."

Christine, Barbara *et al.*, "Cancer in Connecticut, 1969."

Christine, Barbara *et al.*, "Cancer in Connecticut, 1970."

Christine, Barbara *et al.*, "Cancer in Connecticut, 1971."

Christine, Barbara *et al.*, "Cancer in Connecticut, 1972."

Clemmesen, J., "Statistical Studies in the Aetiology of Malignant Neoplasms, *Acta Path. Microbiol. Scand.*, Vol. V, Suppl. 261, 1977.

Cook, P. J., R. Doll, and F. S. Fellingham, "A Mathematical Model for the Age Distribution of Cancer in Man," *Int. J. Cancer, 4,* 93-112, 1969.

Cutchis, P., "Stratospheric Ozone Depletion and Solar Ultraviolet Radiation on Earth," *Science, 184,* 13, 1974.

Cutchis, P., "Estimates of Increase in Skin Cancer Incidence with Time Following a Decrease in Stratospheric Ozone," IDA Paper P-1089, February 1975. Also published as Appendix D, Part 1, Chapter 7, CIAP Monograph 5, Final Report, September 1975.

Cutler, S. J. and J. L. Young, eds., "Third National Cancer Survey-Incidence Data, DHEW Publ. No. (NIH) 75-787, 1975.

Dancig, N. M., "National Review of Ultraviolet Radiation," A. N. Sysin Institute of General and Community Hygiene of The Academy of Medical Science of the USSR, 1977.

Davis, J. N. P., "Cancer in Africa," in *Modern Trends in Pathology,* D. H. Collins, ed., Butterworth Medical Publications, London, pp. 132-160, 1959.

Davis, Neville C. *et al.*, "Malignant Melanoma in Queensland, Analysis of 400 Skin Lesions," *The Lancet, 2,* August 20, 1966.

Doll, R., C. Muir, J. Waterhouse, eds., *Cancer Incidence in Five Continents, Volume II,* Springer-Verlag, Berlin, 1970.

Doll, R., In: Waterhouse, J., C. Muir, P, Correa, and Jean Powell, eds., *Cancer Incidence in Five Continents, Volume III,* Lyon, (IARC Scientific Publications No. 15) 1976.

Donovan, J. W., "Do Polyunsaturated Fats Predispose to Malignant Melanoma?," *The Medical Journal of Australia,* August 21, 1976.

Dopplick, Th. G., "Radiative Heating of The Global Atmosphere," *J. Atmos. Sci., 29,* 1278-1294, 1972.

Dunn, J. E., E. A. Levin, G. Linden, and L. Harzfeld, "Skin Cancer as a Cause of Death," *Calif. Med., 102,* 361-363, 1965.

Eisenberg, H., "Cancer Incidence in Connecticut, Incidence and Rates, 1935-1962," Connecticut State Department of Health, 1966.

Eisenhart, C. *et al.*, *Selected Techniques of Statistical Analysis*, McGraw-Hill, 1947.

Elwood, J. M., and J. A. H. Lee, "Recent Data on the Epidemiology of Malignant Melanoma," Seminars in Onocology, Volume 2, No. 2, June 1975.

Emmett, Edward A., "Ultraviolet Radiation as a Cause of Skin Tumors," *Critical Reviews in Toxicology, Vol. 2*, Issue 2, September 1973.

Epstein, J. H., "Comparison of the Carcinogenic and Cocarcinogenic Effects of Ultraviolet Light on Hairless Mice," *J. Nat. Cancer Inst., 34*, 741, 1965.

Epstein, J. H., and W. L. Epstein, "A Study of Tumor Types Produced by Ultraviolet Light in Hairless and Hairy Mice," *J. Invest. Dermatol, 41*, 463-473, 1963.

Ericson, J., *Cancer Incidence in Sweden, 1968-1970*, In: Waterhouse, J., C. Muir, P. Correa, and Jean Powell, eds., *Cancer Incidence in Five Continents, Volume III*, Lyon, (IARC Scientific Publications No. 15) 1976.

Fears, T. R. *et al.*, "Skin Cancer, Melanoma, and Sunlight," *American Journal of Public Health, Vol. 66*, No. 5, May 1976.

Forbes, P. D., "Influence of Continued Exposure to Ultraviolet Light on UVL-Induced Tumors," *Proceedings 2nd Annual Meeting American Society Photobiologists, 102*, 1974.

Fredette, Jean-Marc, *Cancer Incidence in Quebec, 1969-1972*, In: Waterhouse, J., C. Muir, P. Correa, and Jean Powell, eds., *Cancer Incidence in Five Continents, Volume III*, Lyon, (IRAC Scientific Publications No. 15) 1976.

Freeman, R. G., and J. M. Knox, "Recent Experience in Skin Cancer," *Arch. Derm*, 101, April 1970.

Gellin, G. A., *et al.*, "Basal Cell Epithelioma: A Controlled Study of Associated Factors," *Advances in Biology of Skin*, W. Montagna and R. L. Dobson, Eds. Oxford, England, and New York, New York: Pergamon Press, Vol. VII, pp. 329-344, 1966.

Gellin, G. A., *et al.*, "Malignant Melanoma, A Controlled Study of Possibly Associated Factors," *Archives of Dermatology, Vol. 99, pp. 44-45, January 1969.*

Goldrick, R. B. *et al.*, "Do Polyunsaturated Fats Predispose to Malignant Melanoma?," *The Medical Journal of Australia,* June 26, 1976.

Gordon, D. *et al.*, "The Epidemiology of Skin Cancer," V.C.N. Blight, Government Printer, New South Wales, 1972.

Green, A. E. S. and T. Mo, "An Epidemiological Index for Skin Cancer Incidence," *Proceedings 3rd Conference on CIAP,* DOT-TSC-OST-74-15, pp. 518-522, 1974.

Green, A. E. S. *et al.*, "The Middle Ultraviolet Reaching the Ground," *Photochem, Photobiol., 19,* 251-259, 1974.

Green, A. E. S. *et al.*, "The Ultraviolet Dose Dependence of Non-Melanoma Skin Cancer Incidence," *Photochemistry and Photobiology, Vol. 24,* pp. 353-362, 1976.

Grier, W. N., "Squamous Cell Carcinoma of the Body and Extremities," *Cancer of the Skin, Biology-Diagnosis-Management, Vol. II,* Chapter 35, W. B. Saunders Company, 1976.

Herron, J., "The Geographical Distribution of Malignant Melanoma in Queensland," *The Medical Journal of Australia,* November 1, 1969.

Jackson, R., "Myths of Cutaneous Malignant Melanoma," *Laval Medical, Vol. 42,* November 1971.

Jensen, O. M. and A. M. Bolander, "Trends in Malignant Melanoma of the Skin," accepted for publication in *World Health Statistics.*

Keeler, C., "Albinism, Xeroderma Pigmentosum and Skin Cancer," *First International Conference on the Biology of Cutaneous Cancer,* Nat. Cancer Institute, Monograph 10, 349, 1963.

Kennedy, D., Commissioner Food and Drugs, Food and Drug Administration, Dept. of Health, Education and Welfare, "Draft Environmental Impact Statement, Fluocarbons: Environmental and Health Implications," May 1977.

Kripke, M. L., "Immunologic Parameters of UV Carcinogenesis," *International Conference on Ultraviolet Carcinogenesis*, Airlie House, Warrenton, Virginia, March 21-23, 1977.

Lancaster, H. O., "Some Geographical Aspects of the Mortality From Melanoma in Europeans," *Med. J. of Australia, 1*, 1082-1087, 1956.

Lancaster, H. O. and J. Nelson, "Sunlight as a Cause of Melanoma: A Clinical Survey," *The Medical Journal of Australia*, April 6, 1957.

Latarjet, R., "Influence des Variations de L'Ozone Atmospherique sur L'Activite Biologique cu Rayonnement Solaire," *Rev. d'Opt. Theor, et Instr., 14*, 398-414, 1935.

Lea, A. J., "Malignant Melanoma of the Skin: The Relationship to Trauma," *Ann. Roy. Coll. Surg., 37*, 169-176, 1965.

Lee, J. A. H., "In Melanoma and Skin Cancer," *Proceedings of International Cancer Conference*, Sydney, Australia, 1972.

Lee, J. A. H., "Current Evidence About the Causes of Malignant Melanoma," *Progress for Clinical Cancer, 6*, 151-161, 1975.

Lee, J. A. H., "The Current Rapid Increase in Incidence and Mortality from Malignant Melanoma in Developed Societies" *Epidemiology of Melanoma, Pigment Cell, Vol. 2*, 414-420, Karger, Basel, 1976.

Lee, J. A. H. and Ann P. Carter, "Secular Trends in Mortality from Malignant Melanoma," *J. Nat'l Cancer Inst., 45*, 91-97, 1970.

Lee, J. A. H. and Gerry B. Hill, "Marriage and Fatal Malignant Melanoma in Females," *American Journal of Epidemiology, 91*, No. 1, 1970.

Lee, J. A. H. and H. J. Issenberg, " A Comparison Between England and Wales and Sweden in the Incidence and Mortality of Malignant Skin Tumours," *J. Cancer, 26*, 59-66, 1972.

Lever, W. F., *Histopathology of the Skin, Ed. 4*, J. B. Lippincott Company, Philadelphia, 1967.

Machta, L. *et al.*, "Erythemal Ultraviolet Solar Radiation and Environmental Factors," U. S. Department of Transportation, Fourth Conference on CIAP, February 1975.

Mackie, B. S., "Malignant Melanoma and Diet," *The Medical Journal of Australia,* May 18, 1974.

Magnus, K., "Epidemiology of Malignant Melanoma of the Skin in Norway With Special Reference to the Effect of Solar Radiation," Excerpta Medica International Congress Series No. 375, Biological Characterization of Human Tumours, Copenhagen, May 13-16, 1975, Excerpta Medica, Amsterdame, ISBN 90 219 0306 7.

Magnus, K., "Prognosis in Malignant Melanoma of the Skin "Significance of Stage of Disease, Anatomical Site, Sex, Age, and Period of Diagnosis," *Cancer, 40,* No. 1, July 1977.

Mason, Thomas J. *et al.*, "Atlas of Cancer Mortality for U. S. Counties: 1950-1969," DHEW Publication No. (NIH) 75-780.

McDonald, E. J., "Epidemiology of Skin Cancer, 1975," *Neoplasms of the Skin and Malignant Melanoma,* Year Book Medical Publishers, Inc., 1976.

McDonald, E. J., "Incidence and and Epidemiology of Melanoma in Texas," *Neoplasms of the Skin and Malignant Melanoma,* Year Book Medical Publishers, Inc., Chicago, 1976.

McDonald, J. E., "Relationship of Skin Cancer Incidence to Thickness of Ozone Layer," *Congr. Rec., 117,* 3493, March 19, 1971.

McGovern, V. J., "Melanoblastoma," *Med. J. Aust, 1,* 139-142, 1952.

McGovern, V. J., "Epidemiological Aspects of Melanoma: A Review," *Pathology, 9,* 233-241, 1977.

Mohs, F. E., "Chemosurgery for the Microscopically Controlled Excision of Skin Cancer," *Proceedings National Cancer Conference, 6,* 517, 1970.

Morton, W. *et al.*, "Skin Cancer and Water Arsenic in Lane County, Oregon," *Cancer, 37,* May 1976.

National Academy of Sciences, National Research Council, "Halocarbons: Environmental Effects of Chlorafluoromethane Release," 1976.

National Cancer Institute, "Third National Cancer Survey: Incidence Data," DHEW Publication (NIH) 75-787, 1975.

O'Beirn, S. F. *et al.*, "Skin Cancer in County Galway, Ireland," *Sixth National Cancer Conference Proceedings*, Philadelphia, Pennsylvania, J. B. Lippincott Co., pp. 489-500, 1968.

Olsen, G., "The Malignant Melanoma of the Skin, New Theories Based on a Study of 500 Cases," *Danish Medical Bulletin*, September, 1967.

Owens, D. W., "The Influence of Heat, Wind and Humidity on UV Injury," *International Conference on Ultraviolet Carcinogenesis*, Airlie House, Warrenton, Virginia, March 21-23, 1977.

Parsons, P. G. *et al.*, "Oncornavirus-Like Particles in Malignant Melanoma and Control Biopsies," *International Journal of Cancer, Vol. 18*, 757-763, 1976.

Pedersen, E., *Cancer Incidence in Norway, 1968-1972*, In: Waterhouse, J., C. Muir, P. Correa, and Jean Powell, eds., *Cancer Incidence in Five Continents, Volume III*, Lyon, (IARC Scientific Publications No. 15) 1976.

Pinckney, E. R., "The Potential Toxicity of Excessive Polyunsaturates," *American Heart Journal, Vol. 85*, Number 6, June 1973.

Popkin, G. L. and C. P. DeFev, Jr., "Basal Cell Epithelioma," *Cancer of the Skin, Biology-Diagnosis-Management, Vol. II*, Chapter 35, W. B. Saunders Company, 1976.

Raymond, L., *Cancer Incidence in Geneva, Switzerland, 1970-1972*, In: Waterhouse, J. C. Muir, P. Correa, and Jean Powell, eds., *Cancer Incidence in Five Continents, Volume III*, Lyon, (IARC Scientific Publications No. 15), 1976.

Ringertz, N., Ed., "Cancer Incidence in Finland, Iceland, Norway, and Sweden, A Comparative Study," *Acta Pathologica et Microbiologica Scandanavia*, Section *A1971*, Supplement No. 224, 1971.

Sanderson, K. V., "Tumors of the Skin," *Textbook of Dermatology*, A. Rook, D. S. Willkinson, and F. J. A. Ebling, eds., Oxford, Blackwell Scientific Publications, p. 1770, 1968.

Saxen, E. A., *Cancer Incidence in Finland, 1966-1970,* In: Waterhouse J., C. Muir, P. Correa, and Jean Powell, eds., *Cancer Incidence in Five Continents, Volume III,* Lyon, (IARC Scientific Publications No. 15) 1976.

Schulze, R., "Increase of Carcinogenic Ultra-Violet Radiation Due to Reduction in Ozone Concentration in the Atmosphere," *Proc. Int. Conf. on Struct., Compos, and Gen. Circ. of the Upper and Lower Atmos. and Possible Anthropogenic Perturbations, Vol. 1,* 493-497, 1974.

Scott, E. L., *et al.,* National Academy of Sciences, *Environmental Impact of Stratospheric Flight,* Appendix C, pp. 171-221, 1975.

Shaw, H. M., *et al.,* "Changing Trends in Mortality From Malignant Melanoma," *Medical Journal of Australia,* July 16, 1977.

Shu, Yeh, "Skin Cancer in Chronic Arsenicism," *Human Pathology, Vol. 4,* No. 1, 469-485, December 1973.

Sirsat, M. V., "Malignant Melanoma of the Skin in Indians," *Indian J. Med. Sci., 6,* 806-813, 1952.

Steinitz, R., *Cancer Incidence in Israel, 1967-1971,* In: Waterhouse J., C. Muir, P. Correa, and Jean Powell, eds., *Cancer Incidence in Five Continents, Volume III,* Lyon, (IARC Scientific Publications No. 15) 1976.

Sutherland, C. M. *et al., Familial Melanoma Pigment Cell, 2,* 421-426, Karger, Basel, 1976.

Swanbeck, G. and Hillström, L., "Analysis of Etiological Factors of Squamous Cell Skin Cancer of Different Locations." *Acta Dermatovener,*

1. "The Lower Limbs," *49*: 427-435, 1969
2. "The Trunk and the Head," *50*: 129-133, 1970
3. "The Arm and the Hand," *50*: 350-354, 1970
4. "Concluding Remarks," *51*: 151-156, 1971

Teppo, L. *et al.,* "Cancer in Finland 1953-1970: Incidence, Mortality, Prevalence," *Acta Pathologica et Microbiologica Scandinavica,* Section A, Supplement 252, 1975.

Teppo, L. *et al.,* "Sunlight as a Risk Factor of Malignant Melanoma of the Skin," accepted for publication in *Cancer.*

Urbach, F., "Geographic Pathology of Skin Cancer," *The Biologic Effects of Ultraviolet Radiation,* (with emphasis on the skin), edited by F. Urbach, Pergamon Press, 1969.

Urbach, F., "Human Skin Cancer Production by UV," Part 1, Chapter 7 of CIAP Monograph 5, *Impacts of Climatic Change on the Biosphere,* Climatic Impact Assessment Program, Department of Transportation, September 1975.

Urbach, F., and R. E. Davies, "Estimate of the Effect of Ozone Reduction in the Stratosphere on the Incidence of Skin Cancer in Man," U. S. Department of Transportation, Fourth Conference on CIAP, February, 1975.

Urbach, F. and J. Scotto, "Incidence of Nonmelanoma Skin Cancer, Part 1, Chapter 5 of CIAP Monograph 5, *Impacts of Climatic Change on the Biosphere,* Climatic Impact Assessment Program, Department of Transportation, September 1975.

Urbach, F. *et al.*, "Ultraviolet Radiation and Skin Cancer in Man," *Advances in Biology of Skin, Vol. 7,* Edited by W. Montagna and R. L. Dobson, Pergamon Press, Oxford, p. 195, 1966.

Urbach, F. *et al.*, "Genetic and Environmental Interactions in Skin Carcinogenesis," *Environment and Cancer* (A Collection of Papers Presented at the Twenty-Fourth Annual Symposium on Fundamental Cancer Research, 1971, at the University of Texas, M. D. Anderson Hospital and Tumor Institute at Houston). The Williams and Wilkins Company, Baltimore, Maryland, pp. 476, 1972.

U. S. Department of Health, Education, and Welfare, Public Health Service, *End Results in Cancer,* Report No. 4, DHEW publ. NIH 73-272, Washington, D. C., 1972.

Wallace, D. C. *et al.*, "Genetic Factor in Malignant Melanoma," *Cancer, 27,* May 1971.

Walton, R. G. and Cox, A. J., "Electrodesicciation of Pigmented Nevi," *Arch. Dermatol., 87,* 342-349, 1963.

Ward, W. H., "Melanoma, Carcinoma of the Skin and Sunlight (Newcastle)," *Australian Journal of Dermatology, 9,* 1967.

Waterhouse, J., C. Muir, P. Correa, and Jean Powell, eds., *Cancer Incidence in Five Continents, Volume III,* Lyon (IARC Scientific Publications No. 15) 1976.

Williams, R. R., and J. W. Horn, "Association Sites With Tobacco and Alcohol Consumption and Socioeconomic Status of Patients: Interview Study from the Third National Cancer Survey,: *J. National Cancer Inst.*, *58*, 525-547, 1977.

Zubiri, A., *Cancer Incidence in Zaragoza, Spain, 1968-1972*, In: Waterhouse, J., C. Muir, P. Correa, and Jean Powell, eds., *Cancer Incidence in Five Continents, Volume III*, Lyon (IARC Publications No. 15) 1976.

APPENDIX A

COMPARISON OF SKIN CANCER INCIDENCE DATA OBTAINED IN A COOPERATIVE SHORT-TERM SURVEY AND A LONG-TERM CANCER REGISTRY

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In a six month other skin cancer survey conducted by the National Cancer Institute during 1971-72 a meticulous effort of canvassing data in dermatologists' offices as well as hospitals in four U.S. cities was accomplished. A paradox of this survey was the very high incidence rates (approximately double) found for Dallas-Fort Worth as compared to the other skin cancer incidence rates reported by E. J. Macdonald for the more southern city of El Paso, Texas on the basis of comparably complete data but accumulated over many years at the Anderson Hospital and Tumor Institute in Houston, Texas.

The following three observations are used to justify a simple model which indicates that a short-term cooperative skin cancer survey is likely to lead to appreciably higher incidence rates than a long-term survey.

1. For the NCI survey, it was reported that "abstractors made periodic visits to physicians' offices, pathology labs, and radiotherapy units to obtain medical and demographic information on all newly diagnosed skin cancers (i.e., basal cell carcinoma and squamous cell carcinoma) occurring during the survey period of 1 September 1971 through 29 February 1972" (F. Urbach and J. Scotto, 1975). In other words, this was a cooperative survey in which cooperating physicians, in an attempt to give the U.S. government the best possible

data on skin cancer incidence, would have been strongly motivated to find skin cancer tumors. It would therefore have been only natural for them to order biopsies for the many clinically marginal cases which, in a more normal course of events, would have been diagnosed at some later time.

2. For the El Paso data, "the median delay from first sympton of skin cancer to first diagnosis is three years" (E. J. Macdonald, 1976), a period of time six times greater than the period of the NCI survey. There is certainly no reason to suspect that this time delay in diagnosis would be any different in Dallas than in El Paso under conditions encountered in normal dermatological practice in the two cities.

3. During the period of the government survey, it could be expected that the residents may also have cooperated, assuming of course, that they had knowledge of the existence of the survey. At the very least, physicians, nurses, and administrative personnel who were aware of the survey could have been motivated to suggest to acquaintances with lesions that they hurry and report for an examination before the survey was over. At the very most, a publicity campaign conducted through the media could have resulted in a huge turnout of patients. From the figures cited above, there were potentially six times the number of skin cancer cases that could have been diagnosed in the six month survey if the entire population had been made aware of the government survey and if each individual with a lesion had patriotically responded.

Let the number of other skin cancer cases diagnosed in a 6-month period by a continuous cancer registry be designated by N_R, and by a 6-month survey by N_S. The latter is given by

$$N_S = N_R + N_A + \alpha\,(6\,N_R - N_A) \quad , \qquad (A.1)$$

where N_A is the additional number of cases that are diagnosed solely as a result of the added diligence of the physicians in ordering biopsies on those patients who normally would have visited in the absence of a survey. The term $6\ N_R - N_A$ represents the potential pool of patients who had undiagnosed skin cancer lesions at the time of the survey and who normally would have had their skin cancers diagnosed subsequent to the 6-month survey period. The constant α represents the fraction of those potential patients who somehow became informed of the survey, visited a physician for an examination, and received an earlier diagnosis than they otherwise would have received.

The ratio of the survey skin cancer incidence I_S to the continuous cancer registry incidence I_R is given by

$$\frac{I_S}{I_R} = \frac{N_S}{N_R}$$

$$= 1 + \frac{N_A}{N_R} + \alpha \left(6 - \frac{N_A}{N_R}\right) \quad . \qquad \text{(A.2)}$$

Setting $\frac{I_S}{I_R} = 2$ in accordance with the Dallas-El Paso incidence discrepancy, and solving for α,

$$\alpha = \frac{1 - \frac{N_A}{N_R}}{6 - \frac{N_A}{N_R}} \qquad \text{(A.3)}$$

Any combination of the parameters α and N_A/N_R satisfying Eq. (A.3), plotted in Fig. A.1, would explain the factor of 2 discrepancy in incidence rates. Thus, for example, if the survey were conducted secretly, i.e., $\alpha = 0$, $N_A = N_R$ would explain the discrepancy. If the diligence of physicians were to be assumed to be independent of whether or not they were participating in a survey, i.e., $N_A = 0$, then a value of $\alpha = 0.17$ would

explain it. Neither of these two extreme cases, however, are likely to have been representative of existing conditions during the Dallas survey. The true parameter values could be determined in a retrospective survey of the Dallas records over a 3-year period following the period of the survey. No publicity campaign was conducted during the Dallas survey, and therefore physicians may well have been diagnosing twice as many cases of skin cancer for essentially the same patient population they would have treated had they not been participating in the survey.

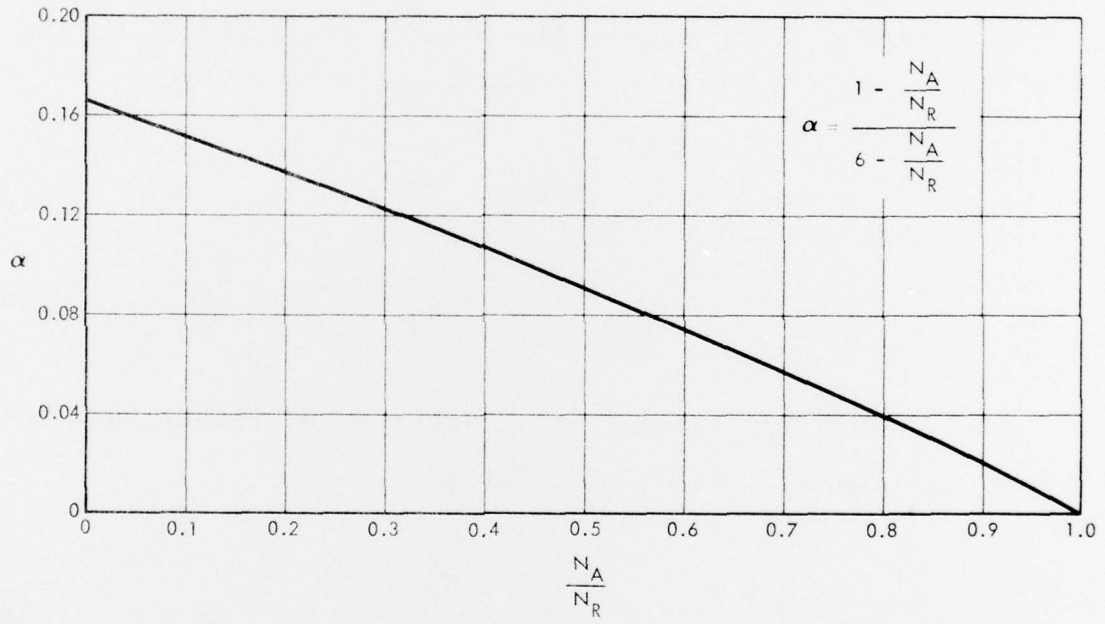

FIGURE A-1. Parameter values explaining the Dallas-El Paso skin cancer incidence rate discrepancy

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